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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/011,394 T 90/011,849	12/17/2010	7,777,074	GASP-004-501	8722

54434 7590 04/02/2014

BOOTH UDALL FULLER, PLC
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EXAMINER	
KUNZ, GARY L	

ART UNIT	PAPER NUMBER
3991	

MAIL DATE	DELIVERY MODE
04/02/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/011,869 + 90011394	08/18/2011	7777074	GASP-004-502	7260

54434 7590 04/02/2014

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MAILED

APR 02 2014

CENTRAL REEXAMINATION UNIT

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. 90/011,394.; 90/011,869

PATENT NO. 7,777,074.

ART UNIT 3991.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/011,394; 90/011,869	Patent Under Reexamination 7,777,074	
	Examiner GARY KUNZ	Art Unit 3991	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a. ☒ Responsive to the communication(s) filed on *June 25, 2013* .
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

b. ☒ This action is made FINAL.

c. ☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire *1* month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *3 - 10* are subject to reexamination.

1b. ☒ Claims _____ are not subject to reexamination.

2. ☒ Claims *1 - 2* have been canceled in the present reexamination proceeding.

3. ☐ Claims _____ are patentable and/or confirmed.

4. ☒ Claims *3 - 10* are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ The drawings, filed on _____ are acceptable.

7. ☐ The proposed drawing correction, filed on _____ has been (7a) ☐ approved (7b) ☐ disapproved.

8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of the certified copies have

1 ☐ been received.

2 ☐ not been received.

3 ☐ been filed in Application No. _____ .

4 ☐ been filed in reexamination Control No. _____.

5 ☐ been received by the International Bureau in PCT application No. _____.

* See the attached detailed Office action for a list of the certified copies not received.

9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.

10. ☐ Other: _____

cc: Requester (if third party requester)

Ex Parte Reexamination: Final Rejection

Procedural Posture

August 16, 2010:	U. S. Patent Application No. 11/950,273 filed December 4, 2007 issued to Kramer et al. as U.S. Patent No. 7,777,074 ("**Kramer '074**").
December 17, 2010:	A first request for ex parte reexamination of claims 1 and 2 of the Kramer '074 patent was filed by Morse, Barnes-Brown & Pendleton, P.C. in Waltham MA. This reexamination was assigned control no. 90/011,394.
January 25, 2011:	Determination granting ex parte reexamination of claims 1 and 2 of Kramer '074 was mailed.
March 25, 2011:	Patent Owner filed a Statement under 37 CFR §1.530.
May 24, 2011:	Third Party Requester filed a Reply to Patent Owner's Statement .
July 21, 2011:	Non-Final Office Action was mailed.
August 18, 2011:	A second request for reexamination of claim 1 of the Kramer '074 patent was filed by Morse, Barnes-Brown & Pendleton, P.C. in Waltham, MA. This ex parte reexamination was assigned control no. 90/011,869.
Sept. 21, 2011:	Patent Owner filed a response to Non-Final Office Action of 7/21/11.
October 7, 2011:	Determination granting ex parte reexamination of claim 1 of Kramer '074 was mailed for 90/011,869.
March 30, 2012:	Decision merging ex parte reexaminations 90/011,394 and 90/011,869 was mailed.
June 26, 2012:	Non-Final Office Action was mailed for merged proceedings.
August 25, 2012:	Patent Owner filed a response to the Non-Final Office Action. Claim 1 was amended. Claim 2 was cancelled. New claims 3 – 10 were added.
February 11, 2013:	Patent Owner filed a Supplemental Response in order to comply with 37 CFR §1.530(f).

February 27, 2013: Final Office Action was mailed indicating that claims 3 - 10 were patentable. Claim 1 was rejected. Claim 2 was canceled.

April 26, 2013: Patent Owner filed a Notice of Appeal.

June 25, 2013: Patent Owner filed an Appeal Brief.

September 12, 2013: Second Non-Final Office Action was mailed.

November 12, 2013: Patent Owner filed an amendment along with §1.132 declarations by Aram M. Petrosyan, Manfred E. Wolff and Richard Chamberlin.

Status of Claims

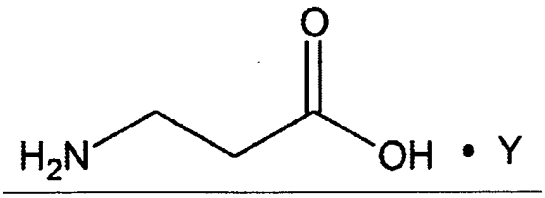
In Patent Owner's Response of November 12, 2013, claims 1 and 2 were cancelled and claims 3 – 10 were amended. Accordingly, amended claims 3 - 10 are under reexamination.

Current Claims

Claim 1. Cancelled.

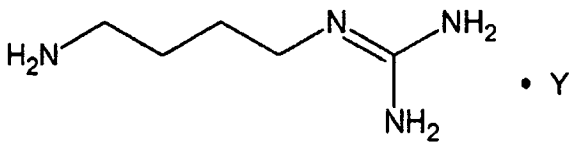
Claim 2. Cancelled.

Claim 3. (New) An Amino Acid Compound having the structure of:



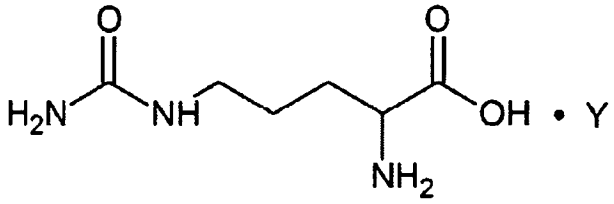
wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Claim 4. (New) A Compound having the structure of:



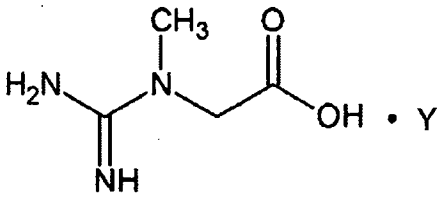
wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Claim 5. (New) An Amino Acid Compound having the structure of:



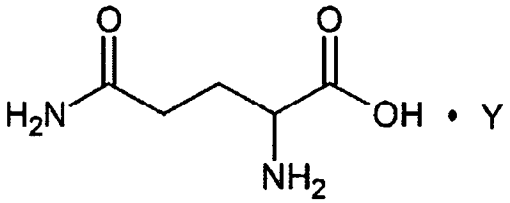
wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Claim 6. (New) A Compound having the structure of:



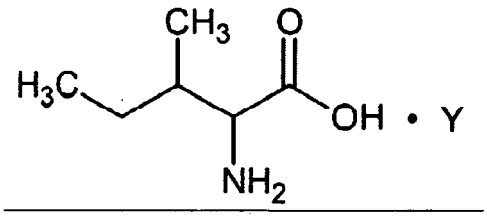
wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Claim 7. (New) An Amino Acid Compound having the structure of:



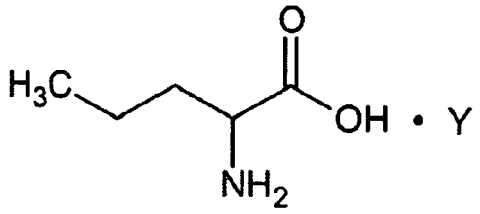
wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Claim 8. (New) An Amino Acid Compound having the structure of:



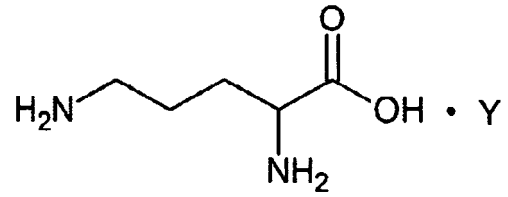
wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Claim 9. (New) An Amino Acid Compound having the structure of:



wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Claim 10. (New) An Amino Acid Compound having the structure of:



wherein Y is selected from the group consisting of a Nitrate and a Nitrite.

Stated more simply:

claim 3 is beta-alanine nitrate or nitrite.
claim 4 is agmatine nitrate or nitrite.
claim 5 is citrulline nitrate or nitrite.
claim 6 is creatine nitrate or nitrite.
claim 7 is glutamine nitrate or nitrite.
claim 8 is isoleucine nitrate or nitrite.
claim 9 is norvaline nitrate or nitrite.
claim 10 is ornithine nitrate or nitrite.

Prior Art Documents of Record

1. McCoy et al., U. S. Patent No. 4,379,177, issued April 5, 1983 ("**McCoy**").

2. Barger, G., The Simpler Natural Bases, R. H. A. Plimmer & F. G. Hopkins (eds.). Monographs on Biochemistry (pages 157 - 163), Longmans, Green & Co., London: 1914 ("**Barger**").

3. Larsen et al., "Effects of dietary nitrate on oxygen cost during exercise," *Acta Physiol.* 191:59 - 66, 2007 ("**Larsen**").

4. Berge et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, 66(1):1 - 18, January 1977 ("***Berge***").

5. Terzyan et al., "L-Arginine nitrates," *Journal of Molecular Structure*, 687:111-117 (2004)("**Terzyan**").

6. Ishii et al., "High glucose augments arginase activity and nitric oxide production in the Renal Cortex," *Metabolism*, 53(7):868 - 974 (July, 2004) ("**Ishii**").

7. Sastre et al., "Metabolism of agmatine in macrophages: modulation by lipopolysaccharide and inhibitory cytokines," *Biochem. J.* 330:1405- 1409 (1998) ("**Sastre**").

8. Harris et al., U. S. Patent No. 5,965,596 issued October 12, 1999 ("**Harris**").

9. Stryer, Lubert, Biochemistry, Third Edition, W. H. Freeman and Company, New York: 1988, pages 16 - 23, 500 - 502 and 934 - 936 ("**Stryer**").

Claim Interpretation

During reexamination, claims are given their broadest reasonable interpretation consistent with the specification and limitations in the specification are not read into the claims (*In re Yamamoto*, 740 F.2d 1569, 222 USPQ 934 (Fed. Cir. 1984)).

The specification of Kramer '074 defines the term "Amino Acid" to include "its physiologically active salts . . . " or "its combinations with various salts . . . " (6:64 to 7:8).

Kramer '074 indicates that the term "Compound" is used to refer to an Amino Acid in combination with one of a Nitrate or a Nitrite (7:9 – 11).

The meaning of the terms "Nitrate" and "Nitrite" is presented at column 7, lines 13 – 46:

> As used herein, "Nitrate" is a term used in its broadest sense and may refer to an Nitrate in its many different chemical forms, including a salt of Nitric Acid, a single administration Nitrate, its physiologically active salts or esters, its combination with its various salts, its tautomeric, polymeric and/or isomeric forms, its analog forms, and/or its derivative forms. Nitrate comprises, by way of non-limiting example, many different chemical forms including dinitrate and trinitrate. Nitrates may be salts, or mixed salts, of Nitric Acid and comprise one Nitrogen atom and three Oxygen atoms. For the exemplary purpose of this disclosure, Nitrate may include mixed salts of Nitrate such as sodium nitrate, potassium nitrate, barium nitrate, calcium nitrate, and the like. For the exemplary purposes of this disclosure, Nitrate may include mixed salts of nitrate orotate, and the like. Additionally, for exemplary purposes of this disclosure, Nitrate may comprise nitrate esters such as nitroglycerine, and the like.
>
> As used herein, "Nitrite" is a term used in its broadest sense and may refer to an Nitrite in its many different chemical forms including a salt of Nitrous Acid, a single administration Nitrite, its physiologically active salts or esters, its combinations with various salts, its tauomeric, polymeric and/or isomeric forms, its analog forms, and its derivative forms. Nitrite comprises, by way of non-limiting example, many different chemical forms including di-nitrite and trinitrite. Nitrites may be salts, or mixed salts, of Nitrous Acid and comprise one Nitrogen atom and two Oxygen atoms. For the exemplary purposes of this disclosure, Nitrite may comprise salts of Nitrite such as sodium nitrite, potassium nitrite, barium nitrite, calcium nitrite, and the like. For the exemplary purposes of this disclosure, Nitrite may comprise mixed salts for Nitrite such as nitrite orotate, and the like. Additionally, for the exemplary purposes of this disclosure, Nitrite may comprise nitrite esters such as amyl nitrite, and the like.

Therefore, according to the descriptive material in column 7, lines 13 – 46, the term "Nitrate" is meant to comprise "many different chemical forms" including mixed salts of amino acids, i.e., neutral and acid salts. Alkali and alkaline earth metal nitrate mixed salts of amino

acids are also encompassed by the general term "Nitrate" of an amino acid. See column 7, lines 22 – 24 where the Patent Owner teaches that Nitrates may be salts or mixed salts such as sodium nitrate, potassium nitrate (alkali metal salts), barium nitrate and calcium nitrate (alkaline earth metal salts).

Amended claims 3 - 10 are interpreted to include mixed nitrate salts with the amino acid or compound because variable "Y" defined as either a nitrate or nitrite does not limit "Y" to a "nitrate anion" or a "nitrite anion" but also encompasses "Y" being a nitrate or nitrite salt such as potassium nitrate or potassium nitrite. If "Y" is limited to a "nitrate anion" or a "nitrite anion," the structure of the compound structure must contain a balancing positive charge on an amino or guanidine group.

Statutory Basis for Claim Rejections

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New Rejection Under 35 USC 112, Second Paragraph

Claims 3 - 10 are rejected under 35 USC 112, second paragraph, for being vague and indefinite.

The chemical structures presented in claims 3 - 10 are indefinite because it is unclear whether the chemical structures encompass mixed salts of the amino acid and metal ion nitric acid salt such as sodium nitrate. In claim 3 for instance, to clearly exclude such mixed salts, "Y" should be designated as either a nitrate anion or a nitrite anion, then the ß-amino group in ß-alanine should be shown as $-NH_3^+$ so that the molecule has a net charge of zero. Alternatively, Y can be defined as a single nitric acid molecule or a single nitrous acid molecule. In this situation, the amino group would not be protonated.

For further clarity the beginning of each claim should specify the name of the molecule as follows:

Claim 3. ß–Alanine nitrate or nitrite having the following structure:
Claim 4. Agmatine nitrate or nitrite having the following structure:
Claim 5. Citrulline nitrate or nitrite having the following structure:
Claim 6. Creatine nitrate or nitrite having the following structure:
Claim 7. Glutamine nitrate or nitrite having the following structure:
Claim 8. Isoleucine nitrate or nitrite having the following structure:
Claim 9. Norvaline nitrate or nitrite having the following structure:
Claim 10. Ornithine nitrate or nitrite having the following structure:

Withdrawn Claim Rejection 102(b)

The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Terzyan has been withdrawn because the Patent Owner cancelled claim 1 in the amendment filed November 12, 2013.

Maintained Claim Rejection 103(a)

Claims 5 - 8 and 10 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over McCoy in view of Stryer.

Amended claims 5 – 8 and 10 still encompass mixed salts of citrulline, creatine, glutamine, isoleucine, and ornithine with a metal nitrate salt.

As explained above in the "Claim Interpretation" section, the term "Nitrate" as it applies to the amino acids in Kramer '074 encompasses any and all types of nitrate salts and mixed salts of an amino acid, i.e., neutral or acidic nitrate salts (7:13 - 30). For example, "Nitrate" may be an alkali nitrate salt (sodium or potassium nitrate) or alkaline earth metal nitrate salt (barium or calcium nitrate) (7:23 - 26). McCoy discloses alkali and alkaline earth metal nitrate salts of nutritionally useful amino acids at column 4, lines 32 - 46 that are better tasting, more stable and less hydroscopic than the free amino acid. McCoy specifically cites lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine and cysteine as nutritionally useful amino acids.

McCoy does not expressly teach that arginine, citrulline, creatine, glutamine, isoleucine and ornithine are nutritionally useful amino acids. However, Stryer, a biochemistry textbook, teaches that arginine, citrulline, creatine, glutamine, isoleucine and ornithine are nutritionally useful amino acids. See pages 16 - 23, 500 - 502 and 934 - 936 of Stryer. Arginine, glutamine

and isoleucine are nutritionally useful amino acids because they are required for the synthesis of proteins (Stryer at pages 16 - 23). Citrulline and ornithine are nutritionally useful amino acids because both can be used to synthesize arginine (Stryer at pages 500 - 502). Creatine is a nutritionally useful compound that is used to synthesize creatine phosphate which is an essential source of energy in muscle tissue (Stryer at page 934 - 936). It would have been obvious to the person of ordinary skill in the art at the time of the invention to modify the teachings of McCoy by preparing mixed nitrate salts (using alkali or alkaline earth metal nitrate salts) of amino acids or compounds taught by Stryer to be nutritionally useful because McCoy teaches that such nitrate salts taste better, are more stable and less hygroscopic that the free amino acid. Thus, claims 5 - 8 and 10 are *prima facie* obvious over McCoy in view of Stryer.

This obviousness rejection will be withdrawn when the Patent Owner amends claims 5 – 8 and 10 to unambiguously eliminate mixed salts of the amino acid and a metal nitrate. See the explanation of the rejection under 35 USC 112, second paragraph above.

Maintained Claim Rejection 103(a)

Claim 3 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over McCoy in view of Harris.

Claim 3 is directed to a nitrate or nitrite salt of ß-alanine. McCoy discloses alkali and alkaline earth metal nitrate salts of nutritionally useful amino acids that are better tasting, more stable and less hydroscopic than the free amino acid (4:32 - 46). McCoy specifically cites lysine, tryptophan, methionine; threonine, phenylalanine, leucine, valine, isoleucine, histidine and cysteine as nutritionally useful amino acids (*Id.*). Although McCoy does not list ß-alanine

among the exemplary list of nutritionally useful amino acids, Harris teaches that ß-alanine is a nutritionally useful amino acid that is required for the synthesis of carnosine, a dipeptide which buffers the hydronium ion concentration in muscle tissue during exercise (Abstract, 2:52 - 62). Thus, it would have been obvious to the person of ordinary skill in the art at the time of the invention to prepare ß-alanine nitrate because Harris explains why ß-alanine is a nutritionally useful amino acid while McCoy teaches that nitrate salts of such amino acids are better tasting, more stable and less hygroscopic than the amino acid alone. Thus, claim 3 is *prima facie* obvious over McCoy in view of Harris.

This obviousness rejection will be withdrawn when the Patent Owner amends claim 3 to unambiguously eliminate the mixed salts of ß-alanine and a metal nitrate. See the explanation of the rejection under 35 USC 112, second paragraph above.

Maintained Claim Rejection 103(a)

Claim 4 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over McCoy in view of Ishii.

Claim 4 is directed to a nitrate or nitrite salt of agmatine but still encompasses a mixed salt of agmatine and a metal nitrate salt.

McCoy discloses alkali and alkaline earth metal nitrate salts of nutritionally useful amino acids at column 4, lines 32 - 46 that are better tasting, more stable and less hydroscopic than the free amino acid. McCoy specifically cites lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine and cysteine as nutritionally useful amino acids, but McCoy does not specifically identify agmatine as a nutritionally useful amino acid.

However, Ishii teaches that agmatine is a nutritionally useful amino acid because it may play a regulatory role during inflammation (Ishii, Abstract). It would have been obvious to the person of ordinary skill in the art at the time of the invention to prepare the nitrate salt of agmatine because McCoy describes nitrate salts of nutritionally useful amino acids and agmatine is a nutritionally useful amino acid as taught by Ishii. The motivation to prepare such a nitrate salt is the further teaching by McCoy that such nitrate salts of an amino acid will taste better, have greater stability and be less hygroscopic than the free amino acid. Thus, claim 4 is *prima facie* obvious over McCoy in view of Ishii.

This obviousness rejection will be withdrawn when the Patent Owner amends claim 4 to unambiguously eliminate mixed salts of agmatine and a metal nitrate. See the explanation of the rejection under 35 USC 112, second paragraph above.

Maintained Claim Rejection 103(a)

Claim 8 is rejected under pre-AIA 35 USC 103(a) as being unpatentable over McCoy.

Claim 8 is directed to a nitrate or nitrite of isoleucine. McCoy '277 discloses alkali and alkaline earth metal nitrate salts of nutritionally useful amino acids at column 4, lines 32 - 46 that are better tasting, more stable and less hydroscopic than the free amino acid. McCoy specifically cites lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine and cysteine as nutritionally useful amino acids. It would have been obvious to a person of ordinary skill in the art at the time of the invention to prepare isoleucine nitrate salt because McCoy teaches that isoleucine is a nutritionally useful amino acid and that the nitrate salt will yield a product that is better tasting, more stable and less hygroscopic than

the free amino acid. Thus, claim 8 is *prima facie* obvious over McCoy.

This obviousness rejection will be withdrawn when the Patent Owner amends claim 8 to unambiguously eliminate mixed salts of the isoleucine and a metal nitrate. See the explanation of the rejection under 35 USC 112, second paragraph above.

Maintained Claim Rejection 103(a)

Claim 9 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over McCoy in view of Ishii.

Claim 9 is directed to a nitrate or a nitrite salt of norvaline. McCoy discloses alkali and alkaline earth metal nitrate salts of nutritionally useful amino acids at column 4, lines 32 - 46. McCoy specifically cites the following amino acids--lysine, tryptophan, methionine, threonine, phenylalanine, leucine, valine, isoleucine, histidine and cysteine--as nutritionally useful amino acids (*Id.*).

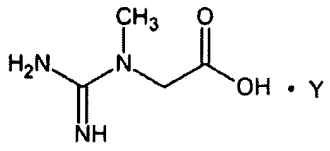
Norvaline is a nutritionally useful amino acid because it is a known inhibitor of arginase, an enzyme which degrades arginine into ornithine and urea (Ishii, Abstract, line 3). By inhibiting arginase, norvaline directs more arginine into the nitric oxide pathway (*Id.*). It would have been obvious to the person of ordinary skill in the art at the time of the invention to prepare the nitrate salt of norvaline because McCoy describes nitrate salts of nutritionally useful amino acids and norvaline is a nutritionally useful amino acid as taught by Ishii. The motivation to prepare such a nitrate salt is the further teaching by McCoy that such nitrate salts of an amino acid are better tasting, more stability and less hygroscopic. Thus, claim 9 is *prima facie* obvious over McCoy in view of Ishii.

This obviousness rejection will be withdrawn when the Patent Owner amends claim 9 to unambiguously eliminate mixed salts of the norvaline and a metal nitrate. See the explanation of the rejection under 35 USC 112, second paragraph, above.

Maintained Claim Rejection 102(b)

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Barger as evidenced by Terzyan.

Claim 6 is directed to creatine nitrate or creatine nitrite whose structure is shown below.



wherein Y must be nitric acid or nitrous acid since the guanidine group is not protonated. If the guanidine group is protonated, then Y is either a nitrate anion or a nitrite anion. The molecular formula for creatine nitrate is: $C_4H_9N_3O_2 \bullet HNO_3$.

Barger discloses the nitrate compound of creatine, i.e., creatine nitrate, at page 160, lines 5 – 6:

> Compounds of creatine.—The *nitrate*, $C_4H_9O_2N_3 .HNO_3$, is less soluble than the hydrochloride or the sulphate. The compounds $C_4H_9O_2N_3 . ZnCl_2$ and $C_4H_9O_2N_3 . CdCl_2 . 2H_2O$ are crystalline (Neubauer [1862, 2]. All these salts are hydrolysed by water.

This passage provides the name of the creatine nitrate mineral acid salt and the molecular formula of creatine nitrate: $C_4H_9O_2N_3 .HNO_3$. At line 6 on page 160, Barger compares creatine nitrate with two additional mineral acid salts of creatine: hydrochloride and the sulphate. With the Barger reference before him, the person of skill in the art in 1914 or 2007

would immediately envision that the nitrate salt of creatine (i.e., creatine nitrate) can be prepared by mixing an aqueous solution containing creatine with an equimolar amount of nitric acid as specified by the molecular formula: $C_4H_9O_2N_3 .HNO_3$. The creatine nitrate would either crystallize out of the solution as the water evaporated or would be deposited as an amorphous solid upon complete evaporation of the water. Claim 6 does not require a crystalline form of creatine nitrate. Consequently, creatine nitrate as claimed in instant claim 6 was placed in the possession of the public on the date that the Barger reference was published—1914.

Withdrawn Claim Rejection 103(a)

The rejection of claims 1, 5 - 8 and 10 under pre-AIA U.S.C. 103(a) as being unpatentable over Terzyan in view of Stryer, Berge and Larsen has been withdrawn for the following reasons.

First, there is an absence of motivation to combine Terzyan with Stryer, Berge and Larsen. Terzyan is a research article that discloses a method for preparing an arginine nitrate but discloses no pharmaceutical properties of arginine nitrate that would motivate a person of skill in the art to prepare similar nitrate salts of other amino acids.

Second, Berge also teaches that only 0.64% of the counter ions in commercially marketed drugs is nitrate. Third, Berge teaches away from using nitrate as the counter ion in pharmaceutical compositions because "nitrate ion causes adverse health effects such as being 'irritating to the GI tract' and causing nausea and gastric distress." See Berge at page 15, left column, last paragraph. See also Wolff Declaration at ¶¶38 - 39. Finally, there is nothing in Terzyan or the other references to motivate the person of skill in the art to prepare the claimed

amino acid nitrate mineral acid salts instead of preparing a simpler mixture of the amino acid with a nitric acid salt such as sodium nitrate.

Withdrawn Claim Rejection 103(a)

Claim 3 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Terzyan in view of Harris, Berge and Larsen.

Claim 3 is directed to ß–alanine nitrate or nitrite.

First, there is an absence of motivation to combine Terzyan with Harris, Berge and Larsen. Terzyan is a research article that discloses a method for preparing an arginine nitrate but discloses no pharmaceutical properties of arginine nitrate that would motivate a person of skill in the art to prepare similar nitrate salts of other amino acids.

Second, Berge also teaches that only 0.64% of the counter ions in commercially marketed drugs is nitrate. Third, Berge teaches away from using nitrate as the counter ion in pharmaceutical compositions because "nitrate ion causes adverse health effects such as being 'irritating to the GI tract' and causing nausea and gastric distress." See Berge at page 15, left column, last paragraph. See also Wolff Declaration at ¶¶38 - 39. Finally, there is nothing in Terzyan or the other references to motivate the person of skill in the art to prepare the claimed ß-alanine nitrate mineral acid salt instead of the simple mixture of the amino acid with a nitric acid salt such as sodium nitrate.

Withdrawn Claim Rejection 103(a)

The rejection of claim 4 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Terzyan in view of Sastre, Berge and Larsen is withdrawn for the following reasons.

First, there is an absence of motivation to combine Terzyan with Stryer, Berge and Larsen. Terzyan is a research article that discloses a method for preparing an arginine nitrate but discloses no pharmaceutical properties of arginine nitrate that would motivate a person of skill in the art to prepare similar nitrate salts of other amino acids.

Second, Berge also teaches that only 0.64% of the counter ions in commercially marketed drugs is nitrate. Third, Berge teaches away from using nitrate as the counter ion in pharmaceutical compositions because "nitrate ion causes adverse health effects such as being 'irritating to the GI tract' and causing nausea and gastric distress." See Berge at page 15, left column, last paragraph. See also Wolff Declaration at ¶¶38 - 39. Finally, there is nothing in Terzyan or the other references to motivate the person of skill in the art to prepare the claimed the agmatine nitrate instead of the simpler mixture of agmatine and a nitric acid salt, such as sodium nitrate.

Withdrawn Claim Rejection - 103(a)

The rejection of claim 9 as being obvious over 35 U.S.C. 103(a) over Terzyan combined with Ishii, Berge and Larsen has been withdrawn for the following reasons.

Claim 9 is directed to norvaline nitrate or norvaline nitrite.

First, there is an absence of motivation to combine Terzyan with Stryer, Berge and Larsen. Terzyan is a research article that discloses a method for preparing an arginine nitrate but discloses no pharmaceutical properties of arginine nitrate that would motivate a person of skill in the art to prepare similar nitrate salts of other amino acids.

Second, Berge also teaches that only 0.64% of the counter ions in commercially marketed drugs is nitrate. Third, Berge teaches away from using nitrate as the counter ion in pharmaceutical compositions because "nitrate ion causes adverse health effects such as being 'irritating to the GI tract' and causing nausea and gastric distress." See Berge at page 15, left column, last paragraph. See also Wolff Declaration at ¶¶38 - 39. Finally, there is nothing in Terzyan or the other references to motivate the person of ordinary skill in the art to prepare the norvaline nitrate mineral acid salt instead of the simple mixture of norvaline and a nitric acid salt such as sodium nitrate.

Response to Patent Owner's Arguments

Patent Owner's Argument:

Page 160 of Barger states the following:

> *Compounds of creatine. – The nitrate, $C_4H_9O_2N_3$. HNO_3 is less soluble than the hydrochloride or the sulphate. The compounds $C_4H_9O_2N_3$. $ZnCl_2$ and $C_4H_9O_2N_3$. $CdCl_2$. $2H_2O$ are crystalline (Neubauer [1862,2]). All the salts are hydrolysed in water.*

The Owner disagrees with the assertion that Barger discloses creatine nitrate as claimed in Claim 6. The Barger passage set forth above and relied upon by the Examiner as evidenced by Terzyan does not demonstrate convincingly that creatine nitrate was a known compound in 1914, that creatine can be made, and that creatine nitrate was in possession of the public before the priority date of the '074 patent.

As described in detail below, the mere naming "the nitrate" of creatine by Barger does not name "creatine nitrate" (it is not the same thing) and mere naming cannot legally constitute a description anyway and is insufficient.

(Patent Owner's Response of 11/12/13 at page 9, lines 10 – 23.)

Examiner's Response:

The Patent Owner asserts that the creatine nitrate as disclosed by Barger on page 160, lines 5 – 9 is not the same as the creatine nitrate as claimed in instant claim 6. However, the molecular formula for the creatine nitrate disclosed on page 160, lines 5 – 6 of Barger is exactly the same as the molecular formula for the creatine nitrate claimed in claim 6: $C_4H_9O_2N_3 . HNO_3$. (The Patent Owner does not deny this fact.) This chemical formula indicates that creatine nitrate consists of one mole of creatine and one mole of nitric acid; that creatine contains four carbon atoms, nine hydrogen atoms, two oxygen atoms and three nitrogen atoms; and that nitric acid contains one hydrogen, one nitrogen and three oxygen atoms. Accordingly, the combined creatine and nitric acid contains four carbon atoms, ten hydrogen atoms, five oxygen atoms and four nitrogen atoms. As further support for the accuracy of this formula at line 5 on page 160 of Barger is the correct chemical structure of creatine at the bottom of page 69 of Barger. The Patent Owner has not provided any evidence to suggest that the molecular formula disclosed by Barger is not identical with the molecular formula for the creatine nitrate claimed in claim 6.

The Patent Owner further argues that the name "nitrate compound of creatine" at line 5 of page 160 of Barger is not the same as "creatine nitrate" without explaining why these two expressions are not the same compound. This argument is not deemed persuasive. The above

passage from Barger not only discloses the name of the same compound as in claim 6--the "nitrate compound of creatine" or "creatine nitrate"--but also provides an accurate molecular formula: $C_4H_9O_2N_3 . HNO_3$, establishing that one mole of creatine is mixed with one mole of nitric acid. It would have been routine even 100 years ago for a chemist to prepare the nitric acid salt of creatine by adding an equimolar amount of nitric acid to an aqueous solution of creatine. Therefore, it is maintained that Barger does much more than merely name the compound of claim 6--it also provides an accurate molecular formula that implicitly teaches the simple method of preparing the nitrate salt of creatine.

Patent Owner's Argument:

All Barger puts in the possession of the public is an inaccurate review that demonstrates that Barger, and/or the reference he relied upon for his review, tried and failed to make "the nitrate" of creatine. (Patent Owner's Response of 11/12/13 at page 9, line 22 to page 10, line 1.)

Examiner's Response:

There is no evidence in Barger or the reference relied upon for the review describing a failed effort to prepare creatine nitrate. Furthermore, the preparation of mineral acid salt, in this case the nitrate salt of creatine, was a routine technique 100 years ago for characterizing compounds containing a basic moiety.

Patent Owner's Argument:

Barger does not provide an enabling disclosure of creatine nitrate, and Terzyan does not either. Therefore, Barger is not a proper and valid prior art reference, and Barger's disclosure, even as evidenced by Terzyan or with the knowledge of one skill in the art, is insufficient to permit the artisan to make creatine nitrate without undue experimentation. (Patent Owner's Response of 11/12/13 at page 10, lines 1 - 5.)

Examiner's Response:

Barger implicitly discloses a method for preparing creatine nitrate which only requires the formation of a nitrate salt of creatine by mixing equimolar amounts of each component as indicated by the molecular formula: $C_4H_9O_2N_3$. HNO_3. The law only requires that the person of skill in the art (2007) at the time of the invention be able to prepare the compound without undue experimentation. Guided by (1) the name of the compound (the nitrate of creatine), (2) the stoichiometry of the molecular formula of the compound ($C_4H_9O_2N_3$. HNO_3) (3) the clear juxtaposition with other mineral acid salts that include the hydrochloride and sulfate salt, (4) the teaching of the crystallization of guanidine-containing compounds (i.e., guanidine nitrate, methyl guanidine nitrate and arginine nitrate from water at page 122, penultimate line to page 123, second line, and (5) the analogy provided by the preparation of creatinine hydrochloride at line 9 – 12 at page 160 of Barger, the person of skill in the art at the time of the invention would have recognized that creatine nitrate could be prepared by simply mixing an aqueous solution of creatine with an equimolar amount of nitric acid. The creatine nitrate would either crystallize from water like arginine nitrate or remain as an amorphous solid after the evaporation of the water. Creatine nitrate was placed in the possession of the public with the disclosure of Barger. To assert otherwise requires that one completely ignore the molecular formula for creatine nitrate and its indicated combination of one mole of creatine with one mole of nitric acid while exaggerating the complexity of preparing creatine nitrate claimed in claim 6. Finally, the Kramer '074 patent discloses that creatine nitrate is prepared by adding an equimolar amount of nitric acid to an aqueous solution of creatine (column 9, lines 4 – 21)--just

as implicitly taught by Barger. The creatine nitrate of instant claim 6 is just the nitric acid (mineral acid) salt of creatine even though the Patent Owner has deleted the name of the compounds from the amended claims. From the chemical structure, instant claim 6 is creatine nitrate has the molecular formula: $C_4H_9O_2N_3 \bullet HNO_3$ or $C_4H_{10}O_2N_3^+ \bullet NO_3^{-1}$, which is equivalent to the molecular formula disclosed by Barger: $C_4H_9O_2N_3 . HNO_3$.

Patent Owner's Argument:

Not only does Barger as evidenced by Terzyan not provide an enabling disclosure, but Barger is also a testament to the significant chemical advancement made by the Owner in the '074 patent. It can be argued, in fact, that the scientific nullity which is the Barger reference (with all its errors and miscues) only further supports the strength of the '074 patent because there is a long felt need for the successful combination of nitrate and creatine. (Patent Owner's Response of 11/12/13 at page 10, line 6 – 11.)

Examiner's Response to Argument:

The Patent Owner argues that Barger in some unspecified manner actually supports a conclusion of a long felt need for a successful combination of nitrate and creatine and that Kramer '074 patent represents a significant chemical advancement. This argument is unfounded. Barger discloses creatine nitrate with a molecular formula of $C_4H_9O_2N_3 . HNO_3$ and its other mineral acid salts--creatine hydrochloride and creatine sulfate at page 160, lines 5 – 6. A person of skill in the art at the time of the invention (2007) would readily recognize that each of these three creatine acid salts can be prepared by mixing an aqueous solution of creatine with an equimolar amount of nitric acid, hydrochloric acid, or sulfuric acid, respectively. Such mineral acid salts of creatine will either crystallize from the water like the nitrate bases disclosed in Barger at page 122, penultimate line to page 123, line 2, or remain as an amorphous solid after the evaporation of the water. Further evidence that the artisan is

capable of preparing nitric acid salts of zwitterions (includes amino acids and creatine) is found in: (1) Rajkumar et al. (of record) which discloses the preparation of both valine nitrate and leucine nitrate (page 1107, left column last three lines through right column, five lines); (2) Petrosyan et al. (of record) discloses the preparation of histidine nitrate (page 160, right column, lines 1 – 5). Rajkumar et al. and Petrosyan et al. each prepared an amino acid nitrate by mixing nitric acid with an equimolar amount of the amino acid dissolved in water and permitting the amino acid nitrate to crystallize from aqueous solution as the water evaporated.

Therefore, as evidenced by Terzyan, Rajkumar et al., Petrosyan et al., the person of skill in the at the time of the invention (2007) would clearly know how to prepare creatine nitrate salt upon reading both the name of the compound along with the molecular formula in Barger at page 160, lines 5 – 6 within the context of being included with two other mineral acid salts. Thus, Barger as evidenced by Terzyan establishes that the creatine nitrate disclosed by Barger was in the possession of the public at the time of the invention in 2007.

Patent Owner's Argument:

"A prior art reference cannot anticipate a claimed invention 'if the allegedly anticipatory disclosures cited as prior art are not enabled.' " Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1354 (Fed. Cir. 2003). "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure' . . . ." In re Hoeksema, 399 F.2d 269 (CCPA 1968).

A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of the invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531 (Fed. Cir. 1985); MPEP 2121.01.

(Patent Owner's Response of 11/12/13 at page 11, lines 5 - 15.)

Examiner's Response:

The examiner completely agrees with the Patent Owner's citation regarding the requirements of an anticipatory reference. In this instance, the public was in possession of creatine nitrate disclosed by Barger because the person or ordinary skill in the art at the time of the invention (2007) could have combined his/her own knowledge to make the claimed invention as required by *Donohue* and MPEP §2121.01. The name of the compound, i.e., "nitrate of creatine," in combination with the molecular formula $C_4H_9O_2N_3 . HNO_3$ and the inclusion of "nitrate of creatine" with the additional two mineral acid salts of creatine, hydrochloride and sulphate salts, would have made it clear to the person of ordinary skill in the art that creatine nitrate can be prepared by mixing equimolar amounts of creatine dissolved in water with nitric acid. The creatine nitrate would either crystallize from solution or be deposited at the bottom of the container after all of the water was evaporated. Terzyan establishes that this same process of preparation is effective for a related guanidine-containing amino acid, arginine.

Patent Owner's Argument:

B. The Claimed Creatine Nitrate or Nitrite Compounds and Structures Are Not Disclosed Identically by Barger

As set forth above in section A. Legal Standards, according to MPEP 2131.01, Terzyan can only be used to show Barger contains an enabled disclosure "[w]hen the claimed composition . . . is ***disclosed identically*** *by the [Barger] reference. In re Samour, 571 F.2d 559 (CCPA 1978) and In re Donohue, 766 F.2d 531 (Fed. Cir. 1985)." As explained below, Barger does not disclose the claimed compounds identically, and, therefore, Barger fails to anticipate the claimed invention regardless of whether or not Terzyan can be used.* (Patent Owner's Response of 11/12/13 at page 13, lines 14 – 22.)

Examiner's Response:

Contrary to the Patent Owner's assertion, Barger discloses the identical compound as that in claim 6 of the Kramer '074 patent. Barger names the same compound: "nitrate of creatine" at page 160, lines 5 – 6; provides the accurate molecular formula: $C_4H_9O_2N_3 . HNO_3$; and includes creatine nitrate alongside of two other creatine mineral acid salts, creatine hydrochloride and creatine sulfate. Given this evidence, Barger unequivocally discloses creatine nitrate as in instant claim 6 of Kramer '074.

Patent Owner's Argument:

1. *Barger Discloses Only a Cocrystalline Mixture of Creatine with a Nitrate Salt*

Page 160 of states the following:

> *Compounds of creatine. – The nitrate, $C_4H_9O_2N_3 . HNO_3$ is less soluble than the hydrochloride or the sulphate. The compounds $C_4H_9O_2N_3 . ZnCl_2$ and $C_4H_9O_2N_3 . CdCl_2 . 2H_20$ are crystalline (Neubauer [1862,2]). All the salts are hydrolysed in water.*

The only reference cited by Barger is to (Neubauer [1862,2]). The disclosure of this cited Neubauer reference is summarized on page 502 of the Exhibit "A Dictionary of Chemistry and the Allied Branches of Other Sciences," Henry Watt, 1872. There we read:

> *"A concentrated aqueous solution of cadmium chloride saturated at 50C with creatine deposits, first unaltered creatine, then by evaporation over sulphuric acid, a compound of creatine with cadmium chloride . . . In the same manner he obtained a compound of creatine with zinc chloride . . . Creatine forms similar compounds with cupric chloride and mercuric nitrate." (Emphasis added.)*

Thus, Neubauer discloses the same two compounds of creatine ($ZnCl_2$ and $CdCl_2$ cocrystallines) and also refers to a chloride (that at the time was used interchangeably with hydrochloride) and a nitrate, namely mercuric nitrate ($HgNO_3$). It would be obvious to someone of ordinary skill in the art or someone that would seek the Neubauer reference that by "the nitrate" of creatine Barger clearly refers to a cocrystalline mixture of creatine with a nitrate salt,

such as $HgNO_3$ (analogous to cocrystalline mixtures of McCoy), and not the Nitrate Salt of creatine as claimed. (Patent Owner's Response of 11/12/13 at page 14, lines 1 - 22.)

Examiner's Response:

The Patent Owner's assertion that the creatine nitrate disclosed by Barger is actually mercuric nitrate described in Neubauer is contradicted by the molecular formula present in Barger at page 160, line 5: $C_4H_9O_2N_3 . HNO_3$. If Barger had intended to describe mercuric nitrate, the reference would have certainly used the symbol for mercury (Hg) in the molecular formula. Barger unambiguously discloses creatine nitrate whose molecular formula establishes an equimolar amount of creatine and nitric acid. Barger does disclose mixed salts of creatine with $ZnCl_2$ and $CdCl_2$ at lines 7 - 9 on page 160 of Barger, but the corresponding molecular formulas also contain the appropriate metal ions. There can be no confusion between creatine nitrate having the molecular formula of $C_4H_9O_2N_3 . HNO_3$ with the Patent Owner proposed mixed salts of creatine and mercury nitrate: $C_4H_9O_2N_3 . HgNO_3$.

Patent Owner's Argument:

2. Mere Naming Insufficient

Mere naming of the subject matter is insufficient, if it cannot be produced without undue experimentation. See Elan Pharm., Inc., v. Mayo Found. For Med. Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003); MPEP 2121.01

Just because Barger mentions a compound, this should not be taken as prior art. On page 160 Barger states: "Compounds of creatine" not "Salts of Creatine." As Dr. Chamberlin declares, "To me it is unclear what compound Barger is referencing when he describes the "nitrate" of creatine. Such a compound could possibly be an ester of creatine with nitric acid, any of several N-nitrated isomers, a simple mixture of creatine with a salt of nitric acid, or something else. Since Barger doesn't accurately describe the structure claimed for creatine nitrate, one well versed in the art reading Barger cannot know what compound he was referring to. Because [of] its substantial ambiguity, Barger should not be accepted as an authoritative

reference of prior art." Richard Chamberlin Declaration ("Chamberlin Declaration") ¶10. (Patent Owner's Response of 11/12/13 at page 15, lines 1 – 14.)

Examiner's Response:

The Patent Owner is attempting to distinguish between a "nitrate compound of creatine" and creatine nitrate. This is a false distinction. The phrase "nitrate of creatine" is equivalent to "creatine nitrate." The Patent Owner and Dr. Chamberlin are dismissing Barger as a credible reference without taking into consideration the molecular formula that is accurate for the nitrate salt of creatine: $C_4H_9O_2N_3 . HNO_3$. The nitrate of creatine is the mineral acid salt of creatine and nitric acid in a molar ratio of 1:1.

The Patent Owner quotes Dr. Chamberlin as suggesting that the term "creatine nitrate" in Barger might refer to a (1) nitrate ester, (2) any of several N-nitrated isomers or (3) a simple mixture of creatine with a salt of nitric acid. The problem with each of these speculative compounds proposed by Chamberlin is that they do not stand up as reasonable options when evaluated against the molecular formula in Barger ($C_4H_9O_2N_3 . HNO_3$) at page 160, line 5.

Since creatine contains no isolated hydroxyl group (such as serine or threonine), there can be no stable nitrate ester of creatine. Any nitrate ester of the carboxylic acid group of creatine would be quite unstable because such a compound would prevent delocalization of electron density of the negative charge of both the carboxyl and nitrate groups. Furthermore, nitrate ester formation is known to require the elimination of a water molecule; thus changing the molecular formula from $C_4H_9O_2N_3 . HNO_3$ to $C_4H_8ON_3 . NO_3$. Accordingly, the molecular formula of creatine nitrate in Barger rules out the more complicated nitrate ester.

Chamberlin further speculates that creatine nitrate could actually be any of several N-nitrated isomers. However, Chamberlin fails to provide the actual chemical structure or molecular formula of such N-nitrated isomers to compare with the molecular formula provided by Barger. The formation of such derivatives would require sophisticated reaction conditions not provided by either Barger or Chamberlin.

Last, Chamberlin asserts that creatine nitrate disclosed by Barger could represent a simple mixture of creatine with a salt of nitric acid. This is not a reasonable option because a salt of nitric acid such as sodium nitrate or potassium nitrate would have a molecular formula containing a metal such as sodium or potassium. The molecular formula of creatine nitrate on page 160 of Barger ($C_4H_9O_2N_3$. HNO_3) does not contain any metal atom.

In conclusion, there is no ambiguity regarding the meaning of creatine nitrate disclosed by Barger on page 160 when interpreted in light of the molecular formula and in the context of two other creatine mineral acid salts: hydrochloride and sulfate.

Patent Owner's Argument:

Moreover, according to Dr. Chamberlin: "Barger is not original research, but rather a summary of the author's understanding of the field at the time (viz, a review article). While it cites a number of original publications, there are no references to any original papers describing creatine or creatinine nitrate. There are instead unreferenced statement regarding the basicity of "the nitrate" of creatine, for example, but by today's standards that does not constitute acceptable evidence for or against the assertion. Furthermore, chemistry at that time was in a very primitive state. There were no modern analytical methods available to prove structures, and even worse, chemical bonding was only beginning to be understood." Chamberlin Declaration ¶5.

Therefore, although Barger says "the nitrate" of creatine, given the primitive stage of chemistry 100 years ago and the difference in terminology, there is no guarantee that the compound given in Barger matches creatine nitrate as claimed by ThermoLife. Barger never states "creatine nitrate." Barger only states "Compounds of creatine" and "the nitrate" of

creatine. This is not identical nor the same thing. As Dr. Chamberlin explained, such a compound could be any number of compounds.

(Patent Owner's Response of 11/12/13 at page 15, line 15 to page 16, line 8.)

Examiner's Response:

It is true that the Barger article is a review article published 100 years ago before modern chemical methods and techniques were developed. However, even 100 years ago chemists were able to perform reliable elemental analysis as evidenced by the numerous compounds disclosed in Barger whose molecular formulas are correct. This is supported by the description of the α-amino acids formed by the hydrolysis of proteins, Δ-amino-valeric acid, ornithine, γ-amino-butyric acid, and glutamic acid in Chapter II and the description of creatine and creatinine in Chapter V. Consequently, the molecular formula $C_4H_9O_2N_3$. HNO_3 should be fully considered in any balanced interpretation of "the nitrate of creatine" of Barger. This molecular formula is the same exact formula for the nitric acid salt of creatine which is claimed in instant claim 6 of the Kramer '074 patent. This molecular formula excludes the speculative alternatives of a nitrate ester; a mixture of creatine and a salt of nitric acid; or an N-nitrated isomers as explained above as explained above.

The meaning of "the nitrate of creatine" described by Barger at page 160, line 5 is further clarified at page 158, last paragraph, where Barger states that creatine salts with minerals acids are hydrolysed by water, which is echoed on page 160, lines 5 – 8. Such salts of creatine prepared with mineral acids (i.e., hydrochloric acid, sulfuric acid and nitric acids) are the same compounds of creatine disclosed by Barger at page 160 at lines 5 and 6: the nitrate,

hydrochloride and the sulfate salts. Even chemists 100 years ago knew how to routinely prepare mineral acid salts of compounds with a basic group such as creatine.

Patent Owner's Argument:

Furthermore, even if Barger did name creatine nitrate (which it does not), the mere naming of "the nitrate" of creatine in Barger cannot constitute a description of the creatine nitrate compound in the '074 Patent and is insufficient because it cannot be produced without undue experimentation. See Manfred E. Wolff Declaration ("Wolff Declaration") ¶23. There should be at least some solid data to back up a prior art claim, and there is absolutely none that has been disclosed or demonstrated in Barger. Barger only provides blanket statements with no detail and no experimental backup. (Patent Owner's Response of 11/12/13 at page 16, lines 9 – 15.)

Examiner's Response:

The meaning of the molecular formula on page 160, line 5 of Barger exactly matches the molecular formula of creatine nitrate of claim 6 and which provides the critical stoichiometry of the reactants: a molar ratio between creatine and nitric acid of 1:1. Accordingly, the disclosure of Barger is not merely the name of the nitrate of creatine, but is also supported by the molecular formula and the solubility comparison with the two other standard mineral acid salts: hydrochloride and sulphate.

The Wolff Declaration asserts that "some solid data should be present to back up the disclosure in Barger" while ignoring the full meaning of the molecular formula. However, the person of ordinary skill in the art at the time of the invention (2007) does not require a detailed method for preparation of a simple mineral acid salt of creatine whose stoichiometry is one mole of creatine to one mole of nitric acid. The artisan would understand that such a salt is prepared by adding an equimolar amount of nitric acid to creatine dissolved in water. Obtaining the product by crystallization or by evaporation of water is consistent with the

teachings about crystallizing guanidine-containing compounds from water in Barger at page 122, last two lines to page 123, line 2. The formation of a mineral salt from a compound containing a basic group is an incredibly simple process: mix an equimolar amount of nitric acid with creatine dissolved in water. The mineral acid salt, creatine, will either crystallize from the water or be left as a solid after the water is completely evaporated. The Kramer '074 patent only describes mixing nitric acid with creatine dissolved in water without even providing the stoichiometric ratio of the reactants (9:29 – 31). Accordingly, there is no undue experimentation required to prepare a simple mineral acid salt of creatine.

Patent Owner's Argument:

3. Ambiguous Reference/Conflicting Statements

"If a reference is ambiguous and can be interpreted so that it may be or may not [sic] constitute an anticipation of an appellant's claims, an anticipation rejection under 35 U.S.C. § 102 based upon the ambiguous reference is improper. In re Brink, 419 F.2d 914, 917 (CCPA 1970)). See also In re Hughes, 345 F.2d 184, 12 (CCPA 1965) ("Moreover, if we accept arguendo the board's position that Link can be alternatively interpreted to show either of two final core structures, then Link becomes an ambiguous reference which will not support an anticipation rejection. In re Turlay, 49 CCPA 1288, 304 F.2d 893, 134 USPQ 355.)

According to Dr. Chamberlin, Barger presents very confusing and ambiguous information. See Chamberlin Declaration ¶¶ 5 - 11, 16 - 19 and 20 - 25.

As just one example, the final sentence of the Barger paragraph cited by the Examiner states: "All these salts [which includes "the nitrate" of creatine] are hydrolyzed by water." Even if "the nitrate" of creatine was actually "creatine nitrate" (which it is not) and had been available, it would not be said "to be hydrolysed" by water. That word means to break a covalent bond with water, and that does not happen to creatine nitrate.

What does this statement mean then? As an example and on the one hand, Barger could have meant to say that it dissolves in water, but then why make the statement at all since the sentence before states that the salts are more or less water soluble. As another example and on the other hand, esters are hydrolyzed by water, so it would appear that Barger understood that the compound that was allegedly made by others to be the ester of creatine with nitric acid.

This one example of clear ambiguity detracts from the credibility of the information in Barger to such a great extent that there is considerable doubt whether "the nitrate" of creatine

was actually "creatine nitrate" and whether creatine nitrate was indeed a known compound when the Barger review was published. But as Dr. Chamberlin expresses all throughout this declaration, it is not just one example. The entire Barger reference is a "scientific nullity" that is completely inappropriate, naïve, inadequate, and ambiguous in its entirety.

(Patent Owner's Response of 11/12/13 at page 16, line 16 to page 17, last line.)

Examiner's Response:

The Patent Owner challenges the value of the Barger reference because of the sentence at page 160, line 8 that states: "All these salts are hydrolysed by water." The Patent Owner interprets the term "hydrolysed" as used in modern chemistry to refer only to process of breaking a covalent bond such as the hydrolysis of an ester into a carboxylic acid and alcohol. This interpretation is contradicted by the molecular formula which is an exact match for the creatine nitrate, a salt of the mineral acid nitric acid, but not for some putative nitrate ester. An ester would require the elimination of a water molecule and would appear as a molecular formula missing one oxygen and two hydrogen atoms. In the context of the disclosure of the entire paragraph on page 160, lines 5 - 8, hydrolysis of a mineral acid of creatine (nitrate, hydrochloride or sulphate) simply refers to the separation of the creatine cation and the nitrate anion in solution. This interpretation is further supported by a similar comment by Barger on page 158, last paragraph: ". . . creatine . . . and its salts with mineral acids are hydrolysed by water. " This statement further underscores that dissolving mineral acid salts of creatine in water merely separates the creatine cation from the nitrate anion.

Patent Owner's Argument:

4. Ambiguous Bonding

"The chemical nature of the bond between creatine and nitrate is unclear in Barger. In his structural formula for creatine, Barger represents what we now understand as covalent bonds with a period or hard stop (".") (see p. 69 of Barger in Appendix B). He later uses this same notation to indicate the chemical relationship between the nitrate and creatine in the nitrate" of creatine (see p. 160, line 5 of Barger). Later in the same paragraph, Barger refers to the "nitrate" of creatine" as a salt that can be "hydrolysed by water" (see p. 160, line 8 of Barger). This formalism was common at the time, before covalent and ionic bonding were well understood, and was thus used as a necessarily vague designation of some sort of bond, complex, or association. It does not define the type of bond, and it further evidences Barger's lack of understanding of the "nitrate" of creatine." Chamberlin Declaration ¶21 (emphasis added.)(Patent Owner's Response of 11/12/13 at page 18, lines 1 – 12.)

Examiner's Response:

The Patent Owner argues that the molecular formula at line 5, page 160 of Barger does not represent creatine nitrate as claimed in claim 6 because the hard stop (".") between the creatine and the nitric acid represents a "vague designation of some sort of bond, complex or association." First of all, despite the hard stop between the α–carbon and the nitrogen attached thereto at the bottom of page 69 of Barger, the molecular formula of creatine ($C_4H_9O_2N_3$) at line 5 at page 160 of Barger is correct and so is the molecular formula for nitric acid (HNO_3). Therefore, this molecular formula specifies that the stoichiometry of the creatine nitrate salt is 1:1. The hard stop between the creatine and the nitric acid in the molecular formula on at line 5, page 160 of Barger, must represent ionic bonding because the mixing of these two compounds will inherently result in what we understand today to be ionic bonds, which is also consistent with Barger designating creatine nitrate as a salt (Barger, page 160, line 8 and page 122, page 158, third line from bottom).

The Patent Owner further argues that the molecular formula at line 5 of page 160 of Barger cannot represent creatine nitrate because of the subsequent statement that "All of these salts are hydrolyzed with water." The Patent Owner then asserts that only esters can be termed "hydrolyzed." These arguments have been fully considered but are not deemed persuasive. First, esters are hydrolyzed by water only in the presence of an acid or base catalyst. Second, the molecular formula at line 5 at page 160 of Barger presents the correct molecular formula for both creatine ($C_4H_9O_2N_3$) and nitric acid (HNO_3). Any putative nitrate ester would require the elimination of a molecular of water which would be reflected in the molecular formula on page 160, line 5 of Barger. Third, Barger designates the product of the reaction of creatine and nitric acid in an equimolar amount as a salt (page 160, line 8 and page 158, third line from bottom). The mixing of an equimolar amount of creatine and nitric acid will inherently result in an ionic bond in the salt. Further, Barger recognized that the reaction of creatine with a mineral acid (nitric acid, hydrochloric acid, or sulphuric acid) in equimolar amounts produced salts which hydrolyzed in water. In this context, hydrolyzed simply means that the creatine cation and nitrate anion separate in water, not that some ester was hydrolyzed, which is not logical. This is because the molecular formula of line 5 of page 160 of Barger does not indicate any loss of a water molecule required by ester formation and because ester hydrolysis requires the presence of an acid or base catalyst not mentioned by Barger. Further, any N-nitrate of creatine as postulated by Chamberlin and Wolff as a possible alternative meaning of the nitrate of creatine at line 5 of page 160 of Barger, would also have a

molecular formula different from the one at line 5 of page 160 and require some complex reaction conditions not described in Barger nor by Chamberlin or Wolff.

Patent Owner's Argument:

Because bonds were not completely understood back in 1914, this only supports the position that Barger is not an enabling reference. The identity of a molecule is inherent in the bonds it contains. If Barger had no idea whether it was a covalent bond or ionic bond or whatever, then how could Barger know that it was creatine nitrate salt? With Barger's further statement that "the nitrate" of creatine is hydrolyzed by water, when only a nitrate ester could be, it is clear Barger does not disclose the claimed compound.

In contrast, the '074 patent discloses a reaction wherein the reactants of an amino group, nitric acid, and water are mixed together, and the product of the reaction includes a new chemical compound—e.g., a nitrate amino group. As is well known in the art, an ionic is formed through an electrostatic attraction between two oppositely charged ions. In the '074 patent, a new compound is formed via ionic bonding, not covalent bonding as Barger apparently teaches. Therefore, the claimed amino acid compound of the '074 patent is different than the unknown and insufficiently described compound listed in Barger that is hydrolyzed in water.

(Patent Owner's Response of 11/12/13 at page 18, line 12 through page 19, line 5.)

Examiner's Response:

The Patent Owner argues that "If Barger had no idea whether it was a covalent bond or ionic bond or whatever, then how could Barger know that it was creatine nitrate salt? First, elemental analysis established that the product of creatine and nitric acid was composed of one mole of creatine and one mole of nitric acid. The type of bond between the two reactants is inherent and does not change if it is not named according to modern bond terminology. Barger states in two places that creatine nitrate is a salt even though the term "ionic bonding" is not used (Barger, page 160, line 8 and page 158, third line from bottom). A salt inherently requires ionic bonding. Finally, when the reactants and reaction conditions are the same, the products must be also be the same.

The Patent Owner states above that the creatine nitrate of instant claim 6 is prepared by mixing an amino group, nitric acid and water together. However, it is more accurate to say that creatine (containing an amino group) is mixed with water and nitric acid. Barger teaches that an equimolar amount of nitric acid is mixed with creatine. Since the same reactants are mixed together in water, then the products must also be the same. Accordingly, the creatine nitrate disclosed by Barger at page 160, line 5 is the same as claimed by instant claim 6.

Patent Owner's Argument:

5. No Structure Disclosed

Here, at least because the structure of the claim compound is not disclosed, Barger does not expressly anticipate or make obvious all of the claimed elements of the claimed invention, and, therefore, the reference cannot be presumed to be operable.
(Patent Owner's Response of 11/12/13 at page 19, lines 7 – 10.)

Examiner's Response:

The correct structure of creatine is shown in Barger at page 69 at the bottom of the page. Accordingly, the molecular formula $C_4H_9O_2N_3$. HNO_3 on page 160, line 5 should be interpreted to mean that creatine and nitric acid are mixed in equimolar amounts to form a mineral acid salt. This is underscored by the next sentence in Barger that groups creatine nitrate with two other mineral acid salts: creatine hydrochloride and creatine sulphate. Accordingly, the teachings of Barger anticipate the simple nitric acid salt of creatine claimed in instant claim 6. The chemist of 100 years, much less the modern chemist of 2007, would, have been able to prepare a mineral acid salt of a compound containing a basic group, such as creatine, by mixing an equimolar amount of nitric acid to an aqueous solution of creatine according to the stoichiometry of the molecular formula of line 5 of page 160 of Barger. The

creatine nitrate of instant claim 6 is nothing more than a mineral acid salt and is prepared the same manner. Thus, the Barger reference anticipates claim 6 and is operable.

Patent Owner's Argument:

Barger teaches the production of creatinine hydrochloride (see p. 160, lines 9 - 13 of Barger), not creatine hydrochloride as incorrectly stated in the Office Action (see p. 14 of the Office Action). See Chamberlin Declaration ¶12 and Wolff Declaration ¶¶ 21-22. The Examiner confirms this in his October 3, 2013 Interview Summary. "While there is a description of how to produce creatinine hydrochloride, this description is not relevant to creatine because of the significant differences between the compounds noted above." Wolff Declaration ¶24.

Creatinine ($C_4H_7N_3O$) and creatine ($C_4H_9N_3O_2$) differ in their chemical structures and their ability to form salts with acidic compounds. Creatinine lacks the carboxyl group present on creatine. As Barger describes on page 158, creatine's "salts" are unstable and get "hydrolysed" by water. Any person of ordinary skill in the art reading Barger would assume that the formation of creatine salts is a much harder thing than forming creatinine salts. See Wolff Declaration ¶22; see also Chamberlin Declaration¶6 ("Barger is thus understandably extremely naive about the nature of ionic bonding and in fact completely unaware that different ionic forms of creatine and/or creatinine even exist (Figure 1), much less have very different properties.") and ¶18 ("Thus, comparing properties without regard for (or certain knowledge of) the exact ionic states can lead to false conclusions. The source of Barger's error was that he did not know the ionic state of the molecules he was studying. It is exactly for this reason that one should ignore assertions regarding similarities in structure or properties unless detailed and irrefutable evidence is presented to support the contention. Similarly, extrapolating properties of a given structure even to others that are superficially similar can be treacherous, as the creatine/creatinine basicity discussion above illustrates.") and ¶9 ("As a result, in describing salts of molecules with multiple proton acceptors one has to be very clear about which ionic form is reacting and what the properties of the product are; if the exact ionic form and counterions of the starting material are not specified (or known), the composition of the product would be unclear. Barger is entirely inadequate as an authoritative reference in this regard.").

Therefore, a person of ordinary skill in the art would certainly not use the production of creatinine hydrochloride as guide as the Examiner states in his Office Action to form creatine nitrate. They are simply very different compounds.
(Patent Owner's Response of 11/12/13 at page 22, line 6 though page 23, line 12.)

Examiner's Response:

The Patent Owner and his declarants (Chamberlin ¶¶ 5 – 11 and 13 – 19 and Wolff at ¶¶21 – 26.) argue that creatine and creatinine are such different compounds that the method for preparing a mineral acid of creatinine (hydrochloride salt) has no analogical value in understanding how to prepare creatine nitrate, also a mineral acid salt. However, even though creatine and creatinine are obviously chemically and structurally different molecules, they have in common the same basic group—an alpha methyl- guanidine. In one instance the methyl guanidine is free (i.e., creatine) whereas in the other instance the methyl guanidine group is cyclized (creatinine).

The Patent Owner is correct that creatine is structurally different than creatinine. Creatine contains a free methyl guanidine group attached to the alpha carbon whereas creatinine contains a cyclic methyl guanidine. In fact, creatinine is formed from creatine by the cyclization of the guanidine to form an amide linkage with the carboxyl group. The only difference between the molecular formulas of creatine and creatinine is a loss of a water molecule from the formula of creatine when the cyclic amide is formed.

Barger groups creatinine with creatine in "Bases of Chapter V" because both of these compounds possess a methyl guanidine group attached to the carbon alpha to the carboxyl. It is instructive to note that Barger consistently discloses the mineral acid salts of the natural bases reviewed in this monograph, not just in Chapter V. Barger treats creatine and creatinine as bases even though creatine is a much stronger base than creatinine. Finally, Barger teaches the nitrate salts of a group of molecules whose only commonality is the basic guanidine group:

guanidine, methyl guanidine, arginine, hypaphorine and certain purine bases can be readily recrystallized from water (Barger, page 122, third line from bottom to page 123, line 2). Since creatine, guanidine, methyl guanidine and arginine each contains a basic guanidine moiety, the person of skill in the art would have had good reason to expect that creatine nitrate would also crystallize from water. But even if the creatine nitrate salt did not crystallize from water, the product of instant claim 6 that would have remained after all of the water was evaporated would still be the creatine nitrate salt. Instant claim 6 does not require crystalline creatine nitrate.

The Patent Owner acknowledges that Barger discloses the production of creatinine hydrochloride at page 160, lines 9 – 13, but Barger implicitly describes the stoichiometry of the reaction of creatinine with hydrochloric acid only as interpreted in the molecular formula: $C_4H_7ON_3$. HCl. In the same manner, lines 5 – 6 of Barger at page 160, also discloses the stoichiometry of the reaction between creatine and nitric acid as an equimolar process according to the molecular formula: $C_4H_9O_2N_3$. HNO_3. The only explicit description in Barger regarding the production of creatinine hydrochloride is the remark that creatinine hydrochloride "separates in anhydrous prisms and tables when a solution of creatinine in hydrochloric acid is evaporated on the water bath; from cold solution it crystallizes with 1 H_2O" (Barger, page 160, lines 9 – 12). The stoichiometric ratios of creatinine to hydrochloride acid is only taught by the molecular formula: $C_4H_7ON_3$. HCl—just as with creatine nitrate in line 5.

The disclosure of the process for preparing creatinine nitrate at page 160, lines 9 - 12, is not required to enable the preparation of creatine nitrate because Barger still discloses

implicitly how to prepare creatine nitrate at lines 5 – 6. The formula for creatine in $C_4H_9O_2N_3$ is correct as is the structure of creatine shown at the bottom of page 69. The formula for nitric acid is also correct: HNO_3. Furthermore, the stoichiometric ratio is 1:1, one mole of creatine per mole of nitric acid. That information alone is enough for the person of skill in the art in 1914 or 2007 to easily prepare creatine nitrate whether or not it crystallizes from water. Claim 6 does not require a crystalline form of creatine nitrate anyway.

In summary, Barger teaches the artisan how to prepare creatine nitrate from the disclosure at page 160, lines 5 - 6 that defines the ratio of reactants as an equimolar amounts of creatine and nitric acid. Furthermore, the disclosure at the bottom of page 122, penultimate line through page 123, line 3 presents a group of other compounds that also contain a basic guanidine group (guanidine, methyl guanidine, arginine, etc.) can be crystallized from water. The person of skill in the art does not require more.

Requiring more of the Barger reference is unfair when the method for preparing creatine nitrate in the Kramer '074 patent discloses even less than Barger. Kramer '074 only states that "Creatine Nitrate [is prepared] by combining nitric acid and Creatine, mixing with water, leaving to crystallize." (Column 9, lines 29 - 31). This "method of preparation" fails to provide a critical element of any preparation: the molar ratio of the reactants. The Kramer '074 patent discloses no melting point, no elemental analysis formula, no nmr data, no color and shape of the crystals. A 102(b) reference is not required to provide more information than the patent under reexamination.

Patent Owner's Argument:

Additionally, creatine is not an amino acid and should not be compared to arginine or other bona fide amino acids. See Aram M. Petrosyan Declaration ("Petrosyan Declaration") ¶12. They are not compounds of the same general class. See Petrosyan Declaration ¶12. They are different and have different properties.

According to Dr. Chamberlin, "This admonition was emphasized by the editor of the monograph in which the oft-cited Barger chapter appears: "The substances described in this monograph do not constitute a homogeneous group. . ." Barger also separated amino acids and creatine into different sections of his monograph [which further makes clear they are not of the same general class]. Specifically, it is evident (see Figure 1 above) that there is not a free amino group substituted on the alpha carbon of creatine, which also lacks a side-chain that is specific to an amino acid. Therefore, creatine and arginine do not belong to the same general class of compound, and their properties differ significantly." Chamberlin Declaration ¶ 13-14; see also Petrosyan Declaration ¶ 12. (Patent Owner's Response of 11/12/13 at page 23, line 10 through page 24, line 2.)

Examiner's Response:

While creatine is not technically amino acid, it is a close relative. Like all amino acids, creatine possess a basic moiety that is on the alpha carbon atom, i.e., a methyl guanidine group. Like the majority of amino acids, creatine is also a zwitterion. Furthermore, like arginine, creatine possesses a strongly basic guanidine group. Consequently, creatine has structural similarities to amino acids generally, and arginine specifically.

It is also instructive to recognize that Barger groups arginine along with guanidine and methyl guanidine at page 122, last two lines and then states that the nitrate salts of these compounds can be crystallized from water. Creatine could also have been grouped with these guanidine-containing compounds because creatine also possesses the defining element: a guanidine moiety.

Patent Owner's Argument:

Petrosyan talks of some of these different properties. Specifically, Petrosyan states: "As is well known, amino acids (with the exception of glycine) possess an asymmetric carbon atom,

giving them two optical isomers and making the study of their optical and crystallographic properties all that more interesting. Creatine does not have any interesting optical properties because it lacks an asymmetrical carbon molecule. That is, there is no D or L form of creatine. Anyone well versed in the art of chemistry and crystallography interested in my job would not find any motivation to synthesize creatine nitrate or any other salt of creatine for this reason alone." Petrosyan Declaration ¶ 3.
(Patent Owner's Response at page 24, lines 3 – 10.)

Examiner's Response:

Dr. Petrosyan argues that because creatine has no asymmetric carbon atom, a person of skill in the art of chemistry and crystallography would have no motivation to synthesize creatine nitrate. This argument is not on point because the outstanding rejection is a 102(b) rejection over Barger--not an obviousness rejection. An anticipation rejection does not require motivation.

Patent Owner's Argument:
Furthermore, Barger teaches that only certain amino acids are bases that could form a salt with an acid. "The process of crystallization, and the properties that control it (primarily solubility) remains today, as it was in 1913, largely an undertaking of trial and error. It is still not possible to accurately predict the solubility of any compound, salt or otherwise, in any solvent.., there is no reliable method of predicting specific solvents that a given salt might crystallize from, or even be soluble in. For this reason, solubility or crystallization behavior cannot be reliably extrapolated from one group of compounds to another." Chamberlin Declaration ¶ 22. (Patent Owner's Response at page 24, lines 11 – 18.)

Examiner's Response:

The Patent Owner's argument is not on point because instant claim 6 does not require the crystalline form of creatine nitrate. This is an argument about a limitation that is not in the claim.

Patent Owner's Argument:
Specifically, "Barger teaches that histidine, lysine, and arginine are basic amino acids and

really the only ones that have an opportunity to form salts by reacting with acids (see p. 33 of Barger in Appendix B)." Wolff Declaration ¶ 25. "A person of ordinary skill in the art reading Barger would interpret these assertions to mean that only the amino acids with two amino groups (i.e., histidine, lysine, and arginine) are bases that could readily react with acids, and certainly citing Barger as precedent for amino acid salt formation should be limited to those three. In fact, the "neutralized" carboxyl group that he refers to actually becomes a weakly basic carboxylate (with the internal ammonium group as counterion), which is now known to be capable of forming salts with very strong acids. The fact that Barger does not recognize this property illustrates how primitive the knowledge of this chemistry was in 1914 and once again suggests great caution in citing Barger as precedent for salt formation." Chamberlin Declaration ¶ 23. (Patent Owner's Response of 11/12/13 at page 24, line 19 through page 25, line 7.)

Examiner's Response:

The Patent Owner's argument ignores the common factor among the basic compounds whose nitrate salt will crystallize from water: guanidine, methyl guanidine, arginine each have a free guanidine moiety as does creatine. Thus, it is entirely reasonable for the artisan to expect creatine nitrate to crystallize from water.

The issue is not how primitive the state of chemistry was in 1914, but whether the compound "nitrate of creatine" disclosed by Barger is, in fact, the creatine nitrate as claimed in instant claim 6. Barger not only provides the correct molecular formula along with the correct stoichiometry, but Barger also refers to creatine nitrate in the same sentence as two associated mineral acid salts, the hydrochloride and the sulphate.

Patent Owner's Argument:

Barger goes on to say that likely only arginine forms a salt with a nitrate and is readily crystallized from water (see pp. 122-123 of Barger in Appendix B)". See Wolff Declaration ¶25. "By naming arginine and not histidine or lysine, Barger further narrows the possibilities of amino acids that could form salts with a nitrate. A skilled artisan reading Barger would not reasonably expect to succeed at crystallizing any nitrate of an amino acid as described except for perhaps arginine nitrate." Chamberlin Declaration ¶ 24. (Patent Owner's Response of 11/12/13 at page 25, lines 8 – 13.)

Examiner's Response:

The Patent Owner is arguing a limitation that is not present in instant claim 6. Claim 6 does not require that the creatine nitrate be in crystalline form. Even if the creatine nitrate did not crystallize from the water, the product remaining after all of the water IS evaporated would still be creatine nitrate as claimed by claim 6.

Patent Owner's Argument:

Anyone skilled in the art reading Barger could not make up his/her mind what the exact compound is that he/she wants to make and will be baffled if asked to make a creatine salt that is "hydrolysed by water", as only a nitrate ester could have. Esters are hydrolyzed by water; salts are dissolved by water. So it would appear that Barger understood the compound that was allegedly made by others to be the ester of creatine with nitric acid. Publishing mistaken information is not prior art; it's publishing a prior mistake. In his review, Barger is not revealing creatine nitrate as prior art; it is unclear what compound he is even revealing. At the very least he is instead blindly publishing an error in the literature from a half-century earlier.

The Chamberlin Declaration confirms this. In paragraph 10, Dr. Chamberlin states: "Furthermore, on page 160 Barger states "Compounds of creatine" not "Salts of Creatine". To me it is unclear what compound Barger is referencing when he describes the "nitrate" of creatine. Such a compound could possibly be an ester of creatine with nitric acid, any of several N-nitrated isomers, a simple mixture of creatine with a salt of nitric acid, or something else. Since Barger doesn't accurately describe the structure claimed for creatine nitrate, one well versed in the art reading Barger cannot know what compound he was referring to. Because its substantial ambiguity, Barger should not be accepted as an authoritative reference of prior art."

Moreover, according to Dr. Chamberlin: "Barger is not original research, but rather a summary of the author's understanding of the field at the time (viz, a review article). While it cites a number of original publications, there are no references to any original papers describing creatine or creatinine nitrate. There are instead unreferenced statements regarding the basicity of "the nitrate" of creatine, for example, but by today's standards that does not constitute acceptable evidence for or against the assertion. Furthermore, chemistry at that time was in a very primitive state. There were no modern analytical methods available to prove structures, and even worse, chemical bonding was only beginning to be understood; it would be several more years (1916) before Gilbert N. Lewis developed the modern concept of the covalent bond and Walther Kossel proposed a theory describing ionic bonds." Chamberlin Declaration ¶5.

Therefore, although Barger says "the nitrate" of creatine, given the primitive stage of chemistry 100 years ago and the difference in terminology, there is no guaranteeing that the compound given in Barger matches creatine nitrate as claimed by ThermoLife. Barger does not include a detailed structure exhibiting the exact compound, a method of production, and a description of the compound/end product and its properties such as shape, color, etc. In fact,

anyone well skilled in the art would be confused by the inconsistencies of the Barger reference. (Patent Owner's Response of 11/12/13 at page 25, line 15 through page 27, line 3.)

Examiner's Response:

The conclusion of Chamberlin that the "nitrate of creatine" as disclosed on page 160, line 5 – 6 is ambiguous and unreliable because it could represent other potential compounds instead of creatine nitrate is faulty because the declarant's evaluation does not take in full account the correct molecular formula for creatine nitrate at line 5 on page 160: $C_4H_9O_2N_3$. HNO_3. The pre-modern chemists could certainly perform elemental analyses of a compound like creatine as shown on page 160, line 5 of Barger. The structure of creatine shown at the bottom of page 69 is correct. The stoichiometry of the reaction between creatine and nitric acid is correct as shown in the molecular formula at line 5 of page 160 of Barger: $C_4H_9O_2N_3$. HNO_3.

Chamberlin's depreciation of Barger fails because the declarant has not proposed any reasonable alternative compounds to creatine nitrate as the proper interpretation of the meaning of the molecular formula at line 5, page 160 of Barger: $C_4H_9O_2N_3$. HNO_3. The molecular formula of a nitrate ester would be reduced by one water molecular that occurs during ester formation. A mixed salt of creatine and an alkali metal or alkaline earth metal fails because the molecular formula disclosed by Barger contains no metal ion. Finally, any putative N-nitrate derivative of creatine would also fail to have the exact same molecular formula and would require a complex set of reaction conditions.

Finally, the Patent Owner deprecates the Barger discloses because the reference does not provide an adequate description of the product such as color, shape, etc. This argument has no merit because the specification of the Kramer '074 discloses so little regarding the same properties of creatine nitrate. A column 9, lines 29 - 31, Kramer '074 entire description of the method for preparing creatine nitrate is to mix the creatine and nitric acid together in water and allow the product to crystallize from the water. The Kramer '074 fails to disclose the color of the product, the shape of the crystals, the nmr data, or even a simple melting point. Finally, Kramer '074 does not even provide the molar ratio of the reactants.

Patent Owner's Argument:

Next, Terzyan does nothing to remedy the deficient disclosure of Barger. The Examiner argues in the Office Action that a person of skill in the art would have been motivated to make creatine nitrate from the teachings of Terzyan. This is simply incorrect.

Dr. Aram M. Petrosyan, the senior co-author on Terzyan, explains how narrowly the research set forth in Terzyan would be viewed by a person of ordinary skill in the art in his Declaration. Dr. Petrosyan describes the difficulty in producing new salts of amino acids:

The formation of new salts of amino acids in stable crystalline form that can be isolated and studied is a tedious job requiring much experimentation, as exhibited from my many works and the difference in methodology to grow a salt. Although the basic premise of combining an acid with a base might seem simple enough, this is certainly not the case. Salts of amino acids hold special challenges, as amino acids possess both an acidic and a basic group, as well as side groups that can be both acidic and basic. Further complications can arise from the existence of other side groups, like alcohols in the cases of serine and threonine, which in the case of nitric acid are documented to form a nitric acid ester rather than a salt. Petrosyan Declaration ¶ 8. Dr. Petrosyan also notes that he and the other co-authors of Terzyan were "focused only on trying to produce crystals in the LAP [L-arginine phosphate] family," and they "did not contemplate any other amino acids, let alone nitrate salts of other amino acids." Petrosyan Declaration ¶¶ 6 - 7.

Given the significant experimentation involved in producing new salts of amino acids, Dr. Petrosyan concludes:

> *It is unreasonable to assume that anyone could be sure after reading our work that they could grow nitrates of other amino acids (and certainly not for creatine, which is not an amino acid to start with). In fact, I believe it would take a lot of experimentation to try and see if a stable nitrate salt could even be made.*

Petrosyan Declaration ¶ 8 (emphasis added). Thus, according to the senior co-author of Terzyan, a person having ordinary skill in the art would find no motivation or suggestion in Terzyan to extend the reported findings related to crystalline forms of L-arginine nitrate compounds to any other amino acid compounds, let alone to unrelated and different classes of compounds, such as creatine for example.

Accordingly, a person of skill in the art would NOT have been motivated to make creatine nitrate from the teachings of Terzyan. As Dr. Petrosyan states: "In the hundreds of studies my group has performed, none was on creatine or its salts. It would, therefore, be unreasonable to assume that anyone interested in crystallography studying the work represented in Terzyan would be motivated to use its teachings to synthesize creatine nitrate, or even assume that this was a logical next step." Petrosyan Declaration ¶ 14.

Examiner's Response:

Dr. Petrosyan argues that Terzyan cannot provide motivation for preparing creatine nitrate because the declarant's laboratory was only interested in investigating the X-ray crystallography of arginine nitrate. However, motivation is only required in an obviousness rejection. The instant rejection of claim 6 is based on anticipation by Barger. Therefore, any argument about motivation is irrelevant.

Dr. Petrosyan further argues that it would require a lot of experimentation to prepare other amino acid nitrate salts. This argument is not deemed persuasive because Dr. Petrosyan is only interested in crystals of amino acid nitrates whereas instant claim 6 of Kramer '074 does not require crystals of creatine nitrate. The mixing of an amino acid with an equimolar amount of nitric acid and then evaporating the water to leave the solid nitrate cannot be deemed as undue experimentation. This fact is support by the preparation of other amino acid nitrates according to this same procedure: (1) preparation of histidine nitrate in Petrosyan et al. (*J. Molecular Structure*, 794: 160 – 167, 2006) and (2) preparation of valine nitrate and leucine nitrate in Rajkumar et al. (*J.* of Raman Spectroscopy, 11: 1107 – 1112, 2000).

Patent Owner's Argument:

Thus, because of the lack of description and even inaccuracies in the disclosure of Barger, one of ordinary skill in the art could not have combined Barger's incomplete and inaccurate disclosure of "the nitrate" of creatine with Terzyan's method of making arginine nitrate (a completely different compound of a different general class) to even begin to try and make creatine nitrate. This combined with an indication that "the nitrate" of creatine is miraculously "hydrolysed by water" (which is impossible for salts like creatine nitrate) would require undue experimentation as Petrosyan declares (see Petrosyan Declaration ¶ 8).

Examiner's Response:

The Barger reference alone anticipates instant claim 6 of the Kramer '074 patent. Terzyan is not required as part of an obviousness rejection or even as evidence in an anticipation rejection because Barger, itself, discloses the preparation of arginine nitrate and states that this product crystallizes from water as do several related guanidine-containing compounds (guanidine and methyl guanidine at page 122, penultimate line through page 123, line 2). While creatine is not an amino acid, it contains a basic guanidine group like arginine, guanidine and methyl guanidine and would be expect to crystallize from water. However, since instant claim 6 is not limited to crystal of creatine nitrate, any solid creatine nitrate that appears after water is evaporated fully meets instant claim 6.

The Patent Owner argues that the fact that Barger states that the salts of creatine are hydrolyzed in water as establishing that the creatine nitrate disclosed by Barger at page 160, lines 5 – 8 must be a nitrate ester because salts are not hydrolyzed, as that word is understood in modern chemistry. This argument has no substance. The creatine nitrate represented by the molecular formula at line 5 of page 160 of Barger, cannot be a nitrate ester because (1) any nitrate ester would require the loss of a water molecule that is not shown in the molecular

formula, and (2) creatine does not contain a free hydroxyl that could yield a stable nitrate ester. The term "hydrolyzes" as used by Barger simply refers to the process of the creatine cation and the nitrate anion separating in water. There is no other reasonable interpretation because Barger calls the creatine nitrate as "salt" in two locations (page 158, third line from bottom and page 160, line 8).

Contrary to the conclusion of the Patent Owner, the preparation of creatine nitrate from the disclosure of Barger does not require undue experimentation but only requires that an equimolar amount of nitric acid is mixed with creatine.

Patent Owner's Argument:
Whatever the case, in no way does Barger as evidenced by Terzyan enable anyone of ordinary skill to decide what compound he is going to make and how to make it. Barger and the references he apparently reviewed/relied on failed to make the compound creatine nitrate and likely only possibly made a nitrate ester of creatine. All of this together precludes a conclusion of anticipation (or obviousness) of creatine nitrate as a matter of law.

Examiner's Response:

Barger alone discloses creatine nitrate (the "nitrate of creatine" and mineral acid salt) at page 160, lines 5 – 8 and implicitly discloses a method for preparing this simple creatine mineral acid salt: mixing an equimolar amount of nitric acid with creatine.

There is no evidence of record to support the Patent Owner's assertion that Barger and references he relied on failed to made the compound creatine nitrate. Quite the contrary, the chemist in 1914 assumed that the person of skill in the art could prepare a mineral acid salt of a basic compound without a detailed protocol because this was a routine way to characterize basic compounds.

D. Long Felt Need for and Unexpected Properties of Creatine Nitrate

1. Long Felt Need

It is telling to Owner and to Dr. Chamberlin that: "the Examiner has not found any other references that mention creatine nitrate (nor have I [Dr. Chamberlin] for that matter), which further confirms that Barger is a scientific nullity." Chamberlin Declaration ¶ 25. Thus, there has been a long felt need for a creatine salt that addresses the problems of creatine (bioavailability, solubility, distribution to muscles, and the like). As set forth previously, Barger is not an enabling disclosure that put creatine nitrate into the possession of the public. And since that publication, for almost 100 years creatine nitrate has not been in the possession of the public until it was disclosed in the '074 patent- the successful combination of nitrate and creatine by ThermoLife.

A company by the name of TwinLab has sold a supplement under the trademark "Creatine Nitrate", but this is just a case of false advertising. An examination of the information on the product label and its website http://www.twinlab.con/product/creatine-nitrate3-fuel%C2%AE) makes it clear that this product does not even contain the compound creatine nitrate. Images of the container and of the product label are set forth below, and the website states that:

> *Creatine Nitrate3 Fuel is powered by 10g CREATx™, an exclusive blend of Creatine Monohydrate and Creatine Magnesium Chelate, combined with a multi-stage carb blend (to help maintain insulin levels already within the normal range), cell-volumizing agents (glutamine peptides), and patented Cinnulin PF™. Then we added our proprietary Nitrate Pump Complex containing nitric oxide precursors for even more dramatic results.*
>
> *So even despite this false advertising use of the name, no party, not even TwinLab, has ever made creatine nitrate.*

Examiner's Response:

The Patent Owner argues that there has been a long felt need in the art for the creatine nitrate as claimed in claim 6. The rejection of claim 6 over Barger as evidenced by Terzyan is an anticipatory rejection and not an obviousness rejection. Secondary considerations of non-obviousness cannot defeat an anticipation rejection.

2. *Unexpected Properties*

A compound and all of its properties are inseparable. Because of the unpredictable nature of chemical reactions, a compound may be very similar in structure to known and existing compounds and yet exhibit very different properties. Beyond a compound's structure, contemplation of its properties is required for a disclosure to be enabling and used in an obviousness determination.

The Federal Circuit has recognized that unexpected superior results from an invention tend to support a finding that the invention was not obvious to a person of ordinary skills in the art. See In re Baxter Travenol Labs, 952 F.2d 388, 392 (Fed. Cir. 1991). The principle may apply most often to the less predictable fields, such as chemistry, where minor changes in a product would yield substantially different results. See In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997).

As far as solubility, Barger comments on the solubilities of several creatine salts, including "the nitrate" which is not clear that even refers to creatine nitrate. However, it is not well defined what work he is actually citing and no data are provided. At any rate, HCl is a smaller molecule than nitrate so basic rules of chemistry would dictate that HCL is more soluble. Nitrate is a bigger molecule and nitrate salts are typically less soluble than HCl salts. This is even more strengthened by the fact that no method of determining solubility or solubility values is given.

Therefore, Barger just states the obvious-- that HCl is a smaller molecule and, thus, more soluble than nitrate. This solubility statement by Barger would certainly not motivate a person of ordinary skill to make creatine nitrate. Instead, since creatine nitrate is less soluble than creatine sulfate or HCl, one wanting to make a soluble salt of creatine would be motivated to make creatine HCl or sulfate.

However, Barger as stated previously does not disclose a structure for creatine nitrate and, other than solubility, makes no description of the additional unexpected properties of creatine nitrate. Properties of creatine nitrate set forth in the '074 patent include: vasodilating characteristics, higher stability in aquatic and acidic environments, better pharmacotechnical properties, higher bioavailability, higher absorption rate, improving delivery to muscle vs. normal creatine, etc. All of these properties of creatine nitrate are not shared by and unexpected when compared to other creatine salts, like citrate for example.

Examiner's Response:

The Patent Owner is asserting unexpected properties of creatine nitrate of claim 6 that include "vasodilating characteristics, higher stability in aquatic and acidic environments, better pharmacotechnical properties, higher bioavailability, higher absorption rates, improved delivery to muscle versus normal creatine." First of all, the rejection of claim 6 over Barger as evidenced by Terzyan is an anticipatory rejection which cannot be overcome by secondary considerations

of non-obviousness. Second, beyond unsubstantiated assertions, the Patent Owner has not presented any data in support of the putative unexpected results. Furthermore, unexpected results require a comparison not just to creatine citrate but also to mixtures of creatine with nitric acid salts. For all of the above reasons, the alleged unexpected results of creatine nitrate are not deemed persuasive.

E. Conclusion

For the reasons set forth above, Barger does not provide an enabling disclosure of creatine nitrate. Barger merely names a compound, "the nitrate" of creatine, which is not the same as stating "creatine nitrate". Barger is also ambiguous, provides no structure or production method even as evidenced by Terzyan, provides ambiguous bonding, and clearly misrepresents the properties of actual creatine nitrate by saying "the nitrate" of creatine can be hydrolyzed by water, which is impossible for creatine nitrate. All Barger puts in the possession of the public is an inaccurate review that demonstrates that the prior art he relied upon possibly tried and clearly failed to make the compound creatine nitrate. For all of these reasons as discussed above, one of ordinary skill in the art could not have combined Barger's woefully inadequate, ambiguous, and wrong description of "the nitrate" of creatine with Terzyan's method of making arginine nitrate (a completely different compound of a different general class).

Thus, Barger clearly is a non-enabled publication, even in view of In Re Antor Media Corporation (Fed. Cir. 2012) (holding that "during patent prosecution, an examiner is entitled to reject claims as anticipated by a prior art publication or patent without conducting an inquiry into whether or not that prior art reference is enabling."). To the extent that Barger is presumptively enabled under In Re Antor Media Corporation, it is clear that one cannot make creatine nitrate from Barger without undue experimentation. The only reason Barger is being cited in this case is because it names a compound called "the nitrate" of creatine, which is not even naming the claimed compound "creatine nitrate", and even if it was, mere naming of a compound is insufficient.

Accordingly, the Owner has met its burden and submitted more than enough rebuttal evidence in the form of three declarations (including one declaration from the senior co-author of the Terzyan publication) proving that Barger as evidenced by Terzyan is not enabling, and, therefore, by law cannot anticipate Claim 6.

Owner respectfully requests that the anticipation rejection of claim 6 be withdrawn.
(Patent Owner's Response of 11/12/13 at page 32, line 12 through page 33, line 16.)

Examiner's Response:

The Patent Owner's arguments are defective because they have been constructed by ignoring several salient facts about Barger: (1) the molecular formula of the "nitrate of creatine" in Barger ($C_4H_9O_2N_3 . HNO_3$) is accurate for both creatine and nitric acid; (2) the molecular formula provides the accurate molar ratio of the reactants, 1:1; and (3) Barger calls "nitrate of creatine" a salt of a mineral acid, i.e., nitric acid (page 158, third line from bottom) in the same grouping as the other two mineral acid salts: hydro-chloride and sulphate (page 160, line 6). The "nitrate of creatine" of Barger is the mineral acid salt of creatine reacted with an equimolar amount of nitric acid as established by the molecular formula: $C_4H_9O_2N_3 . HNO_3$. The hard stop represents what we know today as ionic bonding because Barger calls this compound a salt of creatine (page 158, third line from bottom; page 160, line 8). The creatine nitrate disclosed by Barger is identical to the creatine nitrate of instant claim 6 because both compounds are prepared by mixing creatine with nitric acid.

Response to the Chamberlin Declaration:

¶5. *The Barger reference that features so prominently in this dispute was published as a monograph chapter in 1913 [sic] (1914). It is not original research, but rather a summary of the author's understanding of the field at the time (viz., a review article). While it cites a number of original publications, I find no references to any original papers describing creatine or creatinine nitrate. There are instead unreferenced statements regarding the basicity of the nitrate of creatine, for example, but by today's standards that does not constitute acceptable evidence for or against the assertion. Furthermore, chemistry at that time was in a very primitive state. There were no modern analytical methods available to prove structures, and even worse, chemical bonding was only beginning to be understood; it would be several more years (1916) before Gilbert N. Lewis developed the modern concept of the covalent bond and Walther Kossel proposed a theory describing ionic bonds.*

Examiner's Response:

The law does not require that the Barger reference be original research only that it place the invention in possession of the public art the time of the invention (2007). The fact that in 1914 chemistry was still in a "primitive" state does not permit the reference to be summarily disregarded. Whether the prior art had a modern understanding of chemical bonding does not negate the disclosure of Barger because this reference teaches the person of skill in art how to make the creatine nitrate without undue experimentation. The disclosure of Barger is at least as informative as the specification of Kramer '074 (9: 29 – 31) which fails to describe the molar ratio of reactants and also fails to provide any basic description of the shape of crystals, melting point, color of product, nmr data, etc.

¶6. *Barger is understandably extremely naïve about the nature of bonding and in fact completely unaware that different ionic forms of creatine and/or creatinine even exist (Figure 1), much less have very different properties.*

¶7. Despite their many differences, creatine, creatinine, and amino acids do have some general characteristics in common, in particular their multiple aforementioned pH-dependent ionic forms (Figure 1). The crucial implication of this property is that any one of these molecules is capable of forming a huge number of salts by reaction with acids or bases, depending on which ionic form is reacting. As the Table shows, each of the four compounds actually consists of multiple ionic forms, all of which are classified as "salts." For each charge shown, a myriad of counterions are possible; for instance, the cationic form of creatine (in red), which is the one that would be necessarily have a negatively charged counter-ion, such as chloride, sulfate, monophosphate, acetate, trichloroacetate, nitrate, etc. In contrast, the basic form (in blue) would require a positively charged counter-ion, such as sodium, potassium, ammonium, alkylammonium. etc.

¶8. The point is that "creatine" (as well as every other salt in the table) is actually many possible distinct chemical entities that would have different properties, such as solubility, taste, etc. Barger did not recognize this sort of structural diversity; the creatine that he described was isolated from "muscle juice" and the creatinine from urine, so that the structures of the compounds that he was discussing are not specified.

¶9. A skilled artisan understands that since a salt is the product of an acid-base reaction, there has to be at least one charged group with a counterion. As a result, in describing salts of

molecules with multiple proton acceptors one has to be very clear about which ionic form is reacting and what the properties of the product are; if the exact ionic form and counterions of the starting material are not specified (or known), the composition of the product would be unclear. Barger is entirely inadequate as an authoritative reference in this regard.

Examiner's Response:

The question at issue is whether the person of skill in the art would find sufficient information in Barger to recognize creatine nitrate and to prepare it without undue experimentation. The molecular formula in Barger, page 160, $C_4H_9O_2N_3$. HNO_3, also communicates to the artisan that creatine and nitric acid are mixed in a molar ratio of 1:1. Therefore, creatine nitrate in Barger is clearly a mineral acid salt of nitric acid because of the sentence immediately after the molecular formula groups creatine nitrate with the other two mineral acid salts of creatine: the hydrochloride and the sulphate. Any other interpretation of this passage from Barger requires postulating various other compounds that are contradicted by the molecular formula. See Chamberlin Decl. at ¶10 below.

Moreover, the disclosure in the Kramer '074 patent does not describe any of the ionic forms of creatine that is reacted with nitric acid (9: 29 – 31). The specification just says that creatine and nitric acid are mixed together in water and that the product crystallizes from solution. Accordingly, Kramer '074 shows no concern for specifying the exact ionic state of the creatine that is reacted with the nitric acid. The Patent Owner cannot require more from a reference than the specification discloses. Barger does not have to be an authoritative reference regarding each of the possible ionic forms of creatine, creatinine and arginine as emphasized above by Chamberlin. Barger only needs to disclose the compound and enable the

artisan at the time of the invention (2007) to be able to make the creatine nitrate without undue experimentation. Barger meets this standard.

¶10. Furthermore, on page 160 Barger states "Compounds of creatine: not "Salts of Creatine." To me it is unclear what compound Barger is referencing when he describes the "nitrate" of creatine. Such a compound could possibly be an ester or creatine with nitric acid, any of several N-nitrated isomers, a simple mixture of creatine with a salt of nitric acid, or something else. Since Barger doesn't accurately describe the structure claimed for creatine nitrate, one well versed in the art reading Barger cannot know what compound he was referring to. Because of its substantial ambiguity, Barger should not be accepted as an authoritative reference of prior art.

Examiner's Response:

The ambiguity found in Barger by Chamberlin is a consequence of the declarant ignoring the accurate molecular formula ($C_4H_9O_2N_3 . HNO_3$) at line 5, page 160 of Barger and the context of this "nitrate of creatine" in conjunction with the other two mineral acid salts, the hydrochloride and sulphate, in the same sentence: "The nitrate, $C_4H_9O_2N_3 . HNO_3$, is less soluble that the hydrochloride or the sulphate." This entire sentence can only be interpreted in one reasonable manner: the nitrate of creatine is a simple mineral acid salt just like the other two simple mineral acids salts—hydrochloride and sulphate. Any other interpretation fails to properly consider the molecular formula and the context of the comparison with the other two types of mineral acid salts.

Chamberlin speculates that the "nitrate of creatine" in Barger could represent a nitrate ester of creatine. However, this alternative fails to correspond to the molecular formula because any nitrate ester would necessarily reduce the molecular formula by a water molecular

which is eliminated lost during ester formation. Without a free hydroxyl such as found in serine or threonine, creatine cannot form a stable nitrate ester.

Chamberlin also suggests that the "nitrate of creatine" could be an N-nitrated isomer but fails to provide a chemical structure in order to determine if the N-nitration product corresponds to the proper molecular formula: $C_4H_9O_2N_3 . HNO_3$. Any such N-nitration would require a sophisticated synthesis with the formation and breaking of covalent bonds; a much more complex problem in organic synthesis than the simple formation of a mineral acid salt.

Finally, Chamberlin suggests that the "nitrate of creatine" may represent a mixed salt of creatine and a salt of nitric acid that would require a metal ion. This possibility also falls because the molecular formula in Barger does not contain the requisite metal ion.

¶11. In addition to Barger's overriding ambiguity, there are a number of more specific reasons, which follow, to remove this reference from consideration in this case.
¶12. Barger teaches the production of creatinine hydrochloride (see page 160, lines 9 – 13 of Barger), not creatine hydrochloride as indicated in the Office Action (see p. 14 of the Office Action.

Examiner's Response:

It is correct that "creatine hydrochloride" at page 14 of the Office Action should properly read "creatinine hydrochloride." However, even the creatinine hydrochloride disclosure by Barger reinforces the Examiner's interpretation of "nitrate of creatine" because creatinine hydrochloride is also a simple salt of a mineral acid just like creatine nitrate.

¶13. Creatine is not an amino acid and should not be compared to arginine or other bona fide amino acids. This admonition was emphasized by the editor of the monograph in which the oft-cited Barger chapter appears. "The substances described in this monograph do not constitute a

homogenous group . . . ." Barger also separated amino acids and creatine into different sections of his monograph.

¶14. Specifically, it is evident (see Figure 1 above) that there is not a free amino group substituted on the alpha carbon of creatine, which also lacks a side-chain that is specific to an amino acid. Therefore, creatine and arginine do not belong to the same general class of compound, and their properties differ significantly.

Examiner's Response:

The Patent Owner is correct that creatine is not an amino acid. However, creatine is a very close chemical relative of the amino acid arginine. Like arginine, creatine contains a basic group attached at the alpha carbon. Like arginine, creatine possesses a highly basic guanidine group. Finally, like the neutral amino acids, creatine is also a zwitterion, a molecule that has zero net charge at neutral pH. It is also noteworthy that Barger groups arginine with other guanidine-containing compounds—guanidine, methylguanidine, hypaphorine and certain purine bases—because each of these compounds possesses a guanidine group and reports that the nitrate mineral acid salt of each compound will readily crystallize from water (page 122, penultimate line through page 123, line 2).

The issue of the similarities and differences between creatine and arginine is not pertinent to the finding of anticipation of claim 6 over Barger because the disclosure of arginine nitrate in Terzyan is not essential. By itself, Barger implicitly teaches the artisan how to prepare creatine nitrate by both naming the compound and providing a molecular formula that specifies an equimolar amount of creatine and nitric acid as reactants.

¶15. Creatinine ($C_4H_7N_3O$) and creatine ($C_4H_9O_2N_3$) differ in their chemical structures and their ability to form salts with acidic compounds, i.e., base/acid properties. Creatinine is a weaker base than creatine, at least as base strength is conventionally defined today. For molecules

such as these in which there are both acidic and basic groups, it is very confusing and ambiguous to use both pK_a and pK_b, so the best way to compare acidity and basicity is to look at the pK_a (acidity) of the protonated bases—higher pK_a means that the protonated base is less acidic and therefore the unprotonated form is more basic. So, creatine is the stronger base by a factor of almost 100: pK_a = 11.0 for protonated creatine compared to 9.2 for creatinine (recall that pK_a is a logarithmic scale, so that each difference of 1 pK_a unit equals a factor of 10 in acidity, i.e., hydronium ion concentration).

¶16. Predicting properties, and their "obviousness," of any such salt based on literature precedent—even by those skilled in the art—is profoundly unreliable if the experimental parameters in the original publication are not carefully and completely specified. For instance, not knowing which of the many forms of a given salt was used in the original experiment can result in a misleading or completely erroneous conclusion.

¶17. Barger's discussion of the properties of creatinine (Appendix B at page 159) provides an excellent example of this problem: he incorrectly asserts that creatinine is a stronger base than creatine: "Creatinine solutions have an acrid taste and are hardly alkaline to litmus. The substance is, however, a stronger base than creatine . . . Wood [1903] . . . .' The source of this error, not realized at the time (~1913), is that apparent basicity in such poly-functional molecules is highly dependent on the exact ionic species being studied (which was not well understood in the early 1900s). In this particular case, the basicity of creatinine can appear to be much greater than that of creatine if one happens to compare neutral creatinine (a neutral free base, Figure 1) and neutral creatine (a neutral zwitterion, Figure 1). Even though both are neutral, the most basic moiety in creatine (guanidine group) is already protonated when the molecule is in its neutral form, with its positive charge exactly neutralized by the internal anionic carboxylate group (i.e., an "inner salt," aka zwitterion), leaving the weakly basic carboxylate as the only proton acceptor. In contrast, the chargeless neutral form of creatinine retains a fairly basic nitrogen and would appear to be the more basic of the two, even though the opposite is actually true.

¶18. Thus, comparing properties without regard for (or certain knowledge of) the exact ionic states can lead to false conclusions. The source of Barger's error was that he did not know the ionic state of the molecules he was studying. It is exactly for this reason that one should ignore assertions regarding the similarities in structure of properties unless detailed and irrefutable evidence is presented to support the contention. Similarly, extrapolating properties of a given structure even to other that are superficially similar can be treacherous, as the creatine/ creatinine basicity discussion above illustrates.

¶19. Thus, it is my opinion that Barger should not be relied upon to reject the claims because it is based on information that is too vague from which to draw any firm conclusions.

Examiner's Response:

The fact that creatine is a much stronger base than creatinine is of no consequence with respect to the disclosure of creatine nitrate as a mineral acid salt and its molecular formula (Barger, page 160, lines 5 – 8; page 158, third line from bottom). Barger discloses that both creatine and creatinine can form mineral acid salts (Barger, page 160, lines 5 – 12) and presents correct molecular formulas for each salt. In addition, each molecular formula requires that equimolar amounts of creatine or creatinine is mixed with the appropriate mineral acid.

The prediction of properties of different ionic forms of compounds like creatine and creatinine is not relevant to the anticipatory rejection of instant claim 6 of Kramer '074. The prediction of properties of different ionic forms would only be pertinent in an obviousness rejection based upon 35 USC 103(a). Moreover, the specification of the Kramer' 074 patent fails to specify the ionic forms of creatine as Chamberlin described above as critical (9:29 – 31). The Barger reference discloses at least as much information about the preparation of creatine nitrate as Kramer '074 specification.

Dr. Chamberlin's conclusion that Barger cannot be relied upon as a prior art reference fails to address the full significance of the teachings of Barger regarding creatine nitrate. The molecular formula ($C_4H_9O_2N_3 . HNO_3$) requires reacting equimolar amounts of creatine and nitric acid. This is sufficient information to permit the person of skill in the art to prepare creatine nitrate by mixing an aqueous solution of creatine with an equimolar amount of nitric acid. Whether a crystalline or a powdered forms is immaterial to the anticipation of instant claim 6. In addition, Barger describes creatine nitrate as a mineral acid salt (page 158, third line from bottom; page 160, lines 5 – 8).

¶20. After reviewing Barger, I have been unable to identify any chemical structure corresponding to creatine nitrate or any method for producing creatine nitrate. Without these details in Barger, a person of ordinary skill in the art would not know which compound corresponds to the "nitrate" of creatine or how to synthesize such a compound.

Examiner's Response:

Dr. Chamberlin's concludes that Barger does not disclose creatine nitrate because there is no chemical structure nor method for preparing the same. However, Dr. Chamberlin continues to ignore the full meaning of the molecular formula for creatine nitrate presented at line 5, page 160 of Barger. The molecular formula for creatine is correct ($C_4H_9O_2N_3$) and the molecular formula for nitric acid (HNO_3) is also correct. Furthermore, the molecular formula ($C_4H_9O_2N_3 . HNO_3$) requires reacting equimolar amounts of creatine and nitric acid. Any person of ordinary skill in the art given that much information, is certainly capable of synthesizing a specific mineral acid salt of a known compound, creatine with no additional information. The artisan would immediately envision mixing an equimolar amount of nitric acid with creatine dissolved in water and then recovering of the creatine nitrate by evaporating the water from the solution--whether in crystalline form or powder form. Instant claim 6 is fully met with either form of the creatine nitrate.

¶21. The chemical nature of the bond between creatine and nitrate is unclear in Barger. In his structural formula for creatine, Barger represents what we now understand as covalent bonds with a period or a hard stop (".") (see p. 69 of Barger in Appendix B). He later uses this same notation to indicate the chemical relationship between nitrate and creatine in the "nitrate" of creatine (see p. 160, line 5 of Barger). Later, in the same paragraph, Barger refers to the "nitrate" of creatine as a salt that can be "hydrolyzed by water" (see p. 160, line 8 of Barger). This formalism was common at the time before covalent and ionic bonding were well understood, and was thus uses as a necessarily vague designation of some sort of bond,

complex, or association. It does not define the type of bond, and it further evidences Barger's lack of understanding of the "nitrate" of creatine.

Examiner's Response:

The declarant asserts that the hard stop (" . ") present in the chemical structure of creatine at the bottom of page 69 shows a lack of understanding in 1914 about the exact nature of bonds. This argument does not negate the structure of creatine as shown on page 69. The chemical structure depicts each of the required atoms in creatine and has each atom ordered in proper relationship with all of the other atoms. There was some uncertainty about the bond between nitrogen atom and alpha carbon atom. However, this fact does not warrant a complete dismissal of the chemical structure.

Similarly, the hard stop (" . ") in the molecular formula for creatine nitrate does indicate some uncertainty about the exact nature of this bond. However, the fact that Barger calls this compound a "salt" on page 160, line 8 and at page 158, third line from bottom makes it clear that the hard stop between creatine and the nitric acid represents an ionic bond. This ionic bond is inherently formed when an equimolar amount of creatine is mixed with nitric acid.

¶22. Moreover, Barger teaches away from the invention claimed in the '074 patent. The process of crystallization, and the properties that control it (primarily solubility) remains today, as it was in 1913, largely an undertaking of trial and error. It is still not possible to accurately predict the solubility of any compound, salt or otherwise, in any solvent. Aside from generalizations, such as the rule of thumb that polar compounds and salts are more soluble in water than non-polar compounds are, there is no reliable method of predicting specific solvents that a given salt might crystallization behavior cannot be reliably extrapolated from one group of compounds to another.

Examiner's Response:

Chamberlin emphasizes that despite all of the advances in contemporary chemistry it is not possible to accurately predict the solubility of any compound, salt or otherwise, in any solvent. In other words, the process of crystallizing a compound remains primarily a trial and error effort guided by some basic principles of polarity. This argument is not relevant to the anticipation of claim 6 by Barger. In order to be a competent 102(b) reference, Barger does not need to teach the person of skill in the art how to crystallize creatine nitrate because instant claim 6 is not limited to creatine nitrate in crystalline form. Creatine nitrate as an amorphous solid powder also anticipates claim 6 because this claim embraces both. It is enough that the molecular formula on page 160, line 5 specifies that creatine nitrate is synthesized by mixing equimolar amounts of creatine and nitric acid to form the mineral acid salt.

¶23. Specifically, Barger teaches only that certain amino acids are bases that easily form a salt with an acid. Barger states, "In the monoamino-acids, formed by the hydrolysis of proteins, the acidic properties of the carboxyl-group are neutralized more or less completely by an adjoining amino-group in the α–position, and only the diamino-acids histidine, lysine, and arginine are bases." (see p. 33 of Barger in Appendix B). A person of ordinary skill in the art reading Barger would interpret these assertions to mean that only amino acids with two amino groups (i.e., histidine, lysine, and arginine) are bases that would readily react with acids, and certainly citing Barger as precedent for amino acid salt formation should be limited to those three. In fact, "neutralized" carboxyl group that he refers to actually becomes a weakly basic carboxylate (with the internal ammonium group as counterion), which is now known to be capable of forming salts with strong acids. The fact that Barger does not recognize this property illustrates how primitive the knowledge of this chemistry was in 1913 and once again suggest great caution in citing Barger as precedent for salt formation.

Examiner's Response:

The declarant asserts that great caution should be taken in citing Barger as a precedent for salt formation because 1) at page 33 Barger suggests that only the basic amino acids—lysine, arginine and histidine—would react with acids to form salts and 2) Barger did not recognize that a neutralized carboxyl group actually becomes a weakly basic carboxylate with the internal ammonium group as counterion. This argument has been fully considered but is not deemed persuasive. There is no requirement in the law that Barger must understand the mechanistic details of the formation of creatine nitrate as disclosed by Barger. Barger describes creatine nitrate by name (i.e., nitrate of creatine), provides an accurate molecular formula ($C_4H_9N_3O_2$. HNO_3.) that specifies the stoichiometric relationship between reactants. This is sufficient information for any skilled chemist in 1914 or 2007 to immediately understand how to prepare this product. An equimolar amount of nitric acid is added to the creatine dissolved in water. The product either crystallizes as the water evaporates or remains after the water is completely evaporated. Instant claim 6 does not require crystalline creatine nitrate.

¶24. Barger also teaches that only a select few of the bases that form nitrate salts are easily crystallized from water. Barger explains, "The nitrates of some bases (guanidine, methylguanidine, arginine, hypaphorine, certain purine bases) can be readily crystallized from water and are particularly little soluble in dilute nitric acid" (emphasis added; see pp. 122 – 123 of Barger in Appendix B). A skilled artisan reading Barger would not reasonably expect to succeed at crystallizing any nitrate from an amino acid as described except for perhaps arginine nitrate.

Examiner's Response:

First of all, Barger does not have to disclose how to crystallize creatine nitrate because instant claim 6 contains no such limitation.

Nevertheless, since Barger teaches that the nitrate salts of guanidine, methylguanidine, arginine, hypaphorine, and certain purine bases, and since creatine also contains a basic guanidine group like the other members of this list (pages 122 - 123 of Barger), the person of skill in the art would be surprised if creatine nitrate did not also crystallize from water along with the members of the above list of nitrate salts. Regardless, crystallization of creatine nitrate is a non-issue because instant claim 6 does not require this limitation.

¶25. Upon review of the prosecution of this reexamination proceeding, it is most telling to me that the Examiner has not found any other references that mention creatine nitrate (nor have I for that matter), which further confirms that Barger is a scientific nullity.

Examiner's Response:

Barger is a 100 year-old reference but it is not a scientific nullity as pronounced by Chamberlin. Regardless of the "primitive" state of chemistry in 1914, the person of skill in the art could certainly perform elemental analysis as attested by the consistently accurate molecular formulas disclosed throughout the article, especially the molecular formulas for both creatine ($C_4H_9N_3O_2$) and creatine nitrate ($C_4H_9N_3O_2$. HNO_3) and creatinine hydrochloride ($C_4H_7N_3O$. HCl) at page 160, lines 5 – 9. Accordingly, Barger presents the name of the compound, creatine nitrate; an accurate molecular formula; and the recognition that creatine nitrate is simply a mineral acid salt formed by combining equimolar amounts of creatine and nitric acid. That is sufficient information to make Barger an enabling reference for the 102(b) rejection over instant claim 6 of the Kramer '074 patent.

Response to Declaration by Manfred E. Wolff:

¶21. The Office Action incorrectly states that "Barger does describe the process for preparing the hydrochloride salt of creatine" (see the first full paragraph on p. 14 of the Office Action. Barger actually teaches the production of creatinine hydrochloride. At p. 160, lines 9 – 13 Barger states:

> *Compounds of creatinine. – The hydrochloride, $C_4H_7ON_3$. HCl, separates in anhydrous prisms and tables when a solution of creatinine in hydrochloric acid is evaporated on the water bath; from cold solution it crystallizes with 1 H_2O. It is not precipitated by zinc chloride except in the presence of excess sodium acetate. (emphasis added)*

Examiner's Response:

The declarant is correct that Barger explicitly discloses a method for preparing creatinine hydrochloride and instead of creatine hydrochloride at page 160, lines 9 – 13. However, this same passage from Barger describes the simple process of preparing a mineral acid salt (hydrochloride) by adding an equimolar amount of hydrochloric acid to an aqueous solution of creatinine and then evaporating the water. The person of skill in the art would recognize that as with creatinine, creatine nitrate is prepared by mixing equimolar amounts of nitric acid with creatine dissolved in water. The product of this reaction anticipates instant claim 6 whether or not the creatine nitrate crystallizes or remains as a powder after the evaporation of the water.

¶22. Creatinine ($C_4H_7N_3O$) and creatine ($C_4H_9N_3O_2$) differ in their chemical structures and their ability to form salts with acidic compounds. Creatinine lacks the carboxyl group present on creatine and acts as a stronger base (see the chemical structures below). As Barger describes on pages 6 and 158, creatine is a much weaker base than creatinine and its "salts" are unstable and get "hydrolyzed" by water. Any person of ordinary skill in the art reading Barger would assume that the formation of creatine salts is a much harder thing than forming creatinine salts.

Examiner's Response:

The fact that Barger thought that creatine was a weaker base than creatinine has no bearing on the disclosure of creatine nitrate ($C_4H_9N_3O_2$. HNO_3) at page 160, lines 5 – 8. The molecular formula of creatine nitrate in Barger indicates to the person of skill in the art that creatine nitrate is prepared by reacting an equimolar amount of nitric acid to creatine dissolved in water. Creatine nitrate crystals or powder would remain upon evaporation of the water. Thus, Barger anticipates instant claim 6.

The statement in Barger at line 8 on page 160 that "All these salts are hydrolysed by water." refers to the process of the mineral acid salts of creatine dissociating into the individual ions as opposed to the stability of covalent bonds that do not hydrolyze in water.

¶23. The mere naming "the nitrate" of creatine by Barger does not constitute a description of creatine nitrate and is insufficient because it cannot be produced without undue experimentation. Barger also fails to present the compound's chemical structure or how to make the compound. Instead, Barger provides confusing and ambiguous information that leaves a person of ordinary skill in the art wondering how to synthesize such a compound and what its chemical characteristics should be.

Examiner's Response:

Wolff ignores the molecular formula of creatine nitrate: $C_4H_9O_2N_2$. HNO_3 in Barger at page 160, line 5. This molecular formula not only provides the correct number of atoms of carbon, hydrogen, oxygen and nitrogen in creatine and nitric acid, but also discloses that the molar ratio of creatine to nitric acid is 1:1. Given the molecular formula for creatine nitrate in Barger, the person of skill in the art would immediately envision the titration of creatine dissolved in water with an equimolar amount of nitric acid. The formation of mineral acid salts

of compounds containing at least one basic moiety is a fundamental process in chemistry that does not require the sophistication of organic synthesis because there is no formation or breakage of covalent bonds. The simple formation of the nitrate salt of creatine does not require any undue experimentation.

¶24. Barger does not disclose a chemical structure corresponding to creatine nitrate. While there is a description of how to produce creatinine hydrochloride, this description is not relevant to creatine because of the significant differences between the compounds noted above. A skilled artisan would not know which compound corresponds with the "nitrate" of creatine because no method for producing creatine nitrate is disclosed.

Examiner's Response:

The formation of mineral acid salts of compounds containing a basic moiety is so routine for the person of skill in the art (whether in 1914 or 2007) that a detailed description for preparing such a salt is not required. At page 160, lines 5 – 8, Barger provides the necessary information to enable the preparation of creatine nitrate, especially the molecular formula. All that is required to prepare a specific mineral acid salt of a compound containing a basic group which is soluble in water, is to react the compound with an equimolar amount of the strong mineral acid, in this case, nitric acid. Wolff suggests that the person of skill in the art (2007) would require a detailed method of preparation of a simple salt of a strong acid. Such an assertion is contradicted by the simplicity of the process which does not require either the formation or breakage of a single covalent bond. Furthermore, the specification of Kramer '074 fails to provide more of a method for preparing creatine nitrate than is implicit in Barger (Kramer '074 at 9: 29 – 31). Kramer '074 merely says that creatine should be mixed with nitric

acid in water and then the product precipitates as crystals. Kramer '074 fails to specifically disclose the molar ratio of the reactants. Kramer '074 provides no more information than Barger regarding the process for preparing creatine nitrate.

¶25. Barger teaches that histidine, lysine and arginine are basic amino acids and really the only ones that have an opportunity to form salts by reacting with acids (see p. 33 of Barger in Appendix B). Barger goes on to say that likely only arginine forms a salt with a nitrate and is readily crystallized from water (see pp. 122 – 123 of Barger in Appendix B.)
¶26. Thus, it is my opinion that Barger teaches away from the claimed invention. It doesn't provide a structure for creatine nitrate, let alone a method of making creatine nitrate. Instead, it suggests that only arginine possibly forms a nitrate salt.

Examiner's Response:

The declarant states that Barger teaches away from creatine nitrate by emphasizing that only the three basic amino acids—lysine, arginine, and histidine—will form salts with acids. This argument is not persuasive because a teaching away is only relevant in an obviousness rejection. Instant claim 6 has been rejected under 35 USC 102(b) over Barger.

The declarant arrives at the conclusion that Barger teaches away from the claimed creatine nitrate by ignoring the accurate molecular formula for creatine nitrate at line 5 on page 160 and the chemical structure for creatine at the bottom of page 69. While Barger does not show the chemical structure of creatine nitrate, this reference does provide the correct molecular formula for creatine nitrate ($C_4H_9N_3O_2$. HNO_3) which teaches that creatine nitrate comprises equimolar amounts of creatine and nitric acid. In addition, creatine nitrate is grouped together with both the hydrochloride and sulphate mineral acid salts in line 6, page 160 of Barger. See also page 122, last three lines to page 123, line 2. This is

sufficient information to place creatine nitrate in the possession of the public at the time of the invention. The person of skill in the art reading Barger would immediately envision the method for preparing creatine nitrate by reacting an equimolar amount of nitric acid to a solution of creatine and then evaporating the water to produce nitric acid salt of creatine as claimed in instant claim 6.

Response to Declaration of Aram M. Petrosyan

¶5. I have reviewed the disclosure set forth in Terzyan, to which I am co-author, and can attest that it is a basic research paper. As noted in the first two sentences of the introduction, we as authors were motivated to widen the understanding of compounds within the L-arginine phosphate (LAP) family because of their promising optical and other properties.
¶6. As Terzyan is a basic scientific research paper, we focused only on trying to produce crystals in the LAP family. We chose Arginine for its optical properties. We did not contemplate nor was their motivation for us to extend this basic research to other companies.
¶7. Rather, in Terzyan we describe the synthesis and characterization of two L-arginine nitrate compounds, a hydrocrystal of chemical formula 2(L-Arg•HNO_3)•H_2O and a crystal lacking water of chemical formula L-Arg•2HNO_3 where Arg represents L-arginine. In Terzyan we disclose multiple salts of L-arginine and cite various publications (see pp. 111 and 117 of Terzyan), but we did not contemplate any other amino acids, let alone nitrate salts of other amino acids.

Examiner's Response:

The rejection of instant claim 6 under 35 USC 102(b) over Barger does not require any motivation from Terzyan for preparing other amino acid nitrates. In fact, this anticipation rejection does not even require Terzyan as evidence for the method for preparing arginine nitrate because Barger, itself, discloses the method for preparing arginine nitrate at page 122, last three lines through page 123, line 2.

¶8. The formation of new salts of amino acids in stable crystalline form that can be isolated and studied is a tedious job requiring much experimentation, as exhibited from my many works and the difference in methodology to grow a salt. Although the basic premise of combining an

acid with a base might seem simple enough, this is certainly not the case. Salts of amino acids hold special challenges, as amino acid possess both an acidic and a basic group, as well as side groups that can be acidic or basic. Further complications can arise from the existence of other side groups, like alcohols in the cases of serine and threonine, which in the case of nitric acid are documented to form a nitric acid ester rather than a salt.

Examiner's Response:

Dr. Petrosyan emphasizes the challenges in obtaining stable crystals of amino acid nitrates. However, instant claim 6 is not limited to crystals of creatine nitrate. Any amorphous powder of creatine nitrate will fully meet claim 6. Consequently, the difficulty of preparing crystals of creatine nitrate is of no consequence in the anticipation rejection of claim 6 by Barger. Furthermore, creatine has no free hydroxyls that would permit the formation of a nitrate ester instead of a the creatine nitrate mineral acid salt as suggested by declarant.

¶9. *As set forth in Terzyan, we were uncertain that crystals of nitrate of arginine could even be grown. We specifically noted:*

> *Previously, another modification of L-Arg • HCOOH in space group $P2_1$ from the aqueous solution of arginine and formic acids by slow diffusion of acetonitrile [sic] was prepared. This raised hopes that from aqueous solutions of L-Arg + $nHNO_3$ with $1 < n < 2$ crystals of nitrate of arginine could be grown and indeed there were justified.*

(Terzyan at p. 111, right column, last two sentences; emphasis added.)

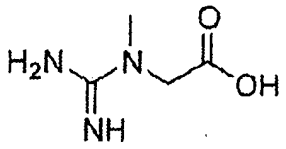
¶10. Even to a person extremely skilled in the art like myself and with all my experience, we were not sure we could isolate crystals of Arginine Nitrate before we experimented. It is unreasonable to assume that anyone could be sure after reading our work that they could grow nitrates of other amino acids (and certainly not for creatine, which is not an amino acid to start with). In fact, I believe it would take a lot of experimentation to try and see if a stable nitrate salt could even be made.
¶11. Thus, to me the foregoing is evidence of how narrowly the research we set forth in Terzyan would be viewed by persons of ordinary skill in the art.

Examiner's Response:

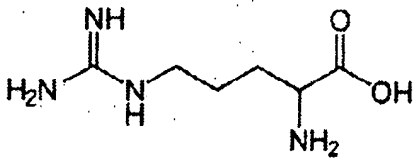
Dr. Petrosyan makes an effective case that the person of skill in the art would not extrapolate the method for preparing arginine nitrate crystals in Terzyan to other amino acids and certainly not creatine. However, this argument is not pertinent to the 102(b) rejection of claim 6 over Barger because claim 6 is not limited to crystals of creatine nitrate.

It is of interest, that in 2000, four years prior to the publication of Terzyan, Rajkumar et al. (*J. Raman Spectrosc.* 31: 1107 – 1112, 2000) reported the preparation of crystals of L-valine nitrate, L-leucine nitrate and L-isoleucine nitrate using the same technique as described by Terzyan: an equimolar amount of nitric acid was mixed with the amino acid dissolved in water; crystals formed during the slow evaporation of the water (Rajkumar et al. at page 1107, left column, second paragraph; page 1107, right column, last full paragraph). Two years after the publication of Terzyan, Petrosyan et al. (*J. of Molecular Structure*, 794: 160 – 167, 2006, of record) workers reported the preparation of crystals of L-histidine nitrate in a manner similar to the synthesis of arginine nitrate, valine nitrate, leucine nitrate and isoleucine nitrate (Petrosyan et al. at page 160, left column, second paragraph; page 160, right column, first paragraph). Consequently, crystals of five different amino acid have been prepared by a similar process: the simple mixing if equimolar amount of nitric acid with the appropriate amino acid dissolved in water. Crystals formed as the water evaporated.

¶12. Creatine is not an amino acid like arginine. From the structures shown below, it is evident that creatine does not possess an amino group connected to the alpha carbon. Creatine also lacks a side-chain that is specific to an amino acid. Therefore, for these reasons and the fact that they have very different properties, creatine and arginine do not belong in the same general class of compounds.



Chemical Structure of Creatine



Chemical Structure of Arginine

¶13. As is well known, amino acids (with the exception of glycine) possess an asymmetric carbon atom, giving them two optical isomers and making the study of their optical properties and crystallographic properties all that more interesting. Creatine does not have any interesting optical properties because it lacks an asymmetrical carbon molecule. That is, there is no D or L form of creatine. Anyone will versed in the art of chemistry and crystallography interested in my job would not find any motivation to synthesize creatine nitrate or any other salt of creatine for this reasons alone.

¶14. In the hundreds of studies my group has performed, none was on creatine or its salts. It would, therefore, be unreasonable to assume that anyone interested in crystallography studying the work represented in Terzyan would be motivated to use its teachings to synthesize creatine nitrate, or even assume that this was a logical next step.

Examiner's Response:

Dr. Petrosyan asserts that the Terzyan article does not provide any motivation for the person of ordinary skill in the art to prepare other amino acid nitrates or creatine nitrate. In addition, since creatine is not an amino acid, the method for preparing arginine nitrate can not be extrapolated to a method for preparing creatine nitrate. Neither of these assertions by Dr. Petrosyan impact the anticipation of instant claim 6 by Barger. The disclosure of Barger at page 160, lines 5 – 9 is sufficient to place creatine nitrate in the possession of the public apart from any method for preparing arginine nitrate described by Terzyan because Barger, itself, discloses

that arginine nitrate along with the nitrate sale of several other guanidine-containing compound (guanidine, methyl guanidine, etc.) crystallize from water (Barger, page 122, last three lines to page 123, line 2).

Conclusion

Claims 1 and 2 are cancelled. Claims 3 – 10 are rejected.

THIS ACTION IS MADE FINAL.

A shortened statutory period for response to this action is set to expire two months from the mailing date of this action.

Extensions of time under 37 CFR 1.136(a) do not apply in reexamination proceedings. The provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Further, in 35 U.S.C. 305 and in 37 CFR 1.550(a), it is required that reexamination proceedings "will be conducted with special dispatch within the Office."

Extensions of time in reexamination proceedings are provided for in 37 CFR 1.550(c). A request for extension of time must specify the requested period of extension and it must be accompanied by the petition fee set forth in 37 CFR 1.17(g). Any request for an extension in a third party requested *ex parte* reexamination must be filed on or before the day on which action by the patent owner is due, and the mere filing of a request will not effect any extension of time. A request for an extension of time in a third party requested *ex parte* reexamination will be granted only for sufficient cause, and for a reasonable time specified. Any request for extension in a patent owner requested *ex parte* reexamination for up to two months from the time period set in the Office action must be filed no later than two months from the expiration of the time period set in the Office action. A request for an extension in a patent owner requested *ex parte* reexamination for more than two months from the time period set in the Office action must be filed on or before the day on which action by the patent owner is due, and the mere filing of a request for an extension for more than two months will not effect the extension. The time for taking action in a patent owner requested *ex parte* reexamination will not be extended for more than two months from the time period set in the Office action in the absence of sufficient cause or for more than a reasonable time.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional month, which will be granted even if previous extensions have been granted. In no event, however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

Extensions of Time

Extensions of time under 37 CFR §1.136(a) will not be permitted in these proceedings because of the provisions of 37 CFR §1.136 apply only to an applicant and not to parties in a reexamination proceeding. Additionally, 35 USC §305 requires that *ex parte* reexamination proceedings "will be concluded with special dispatch" (37 CFR §1.550(a). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR §1.550(c). EXTENSIONS OF TIME WILL NOT BE GRANTED FOR THE PURPOSE OF AN INTERVIEW.

Continuing Duty to Disclose

The Patent Owner is reminded of the continuing responsibility under 37 CFR §§1.555, 1.565(a), and 1.933 to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving U. S. Patent No. 7,777,074 throughout the course of the reexamination proceedings. The Third Party Requester is also reminded of the ability similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§2280 and 2282.

Further Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary L. Kunz, whose telephone number is 571-272-0887. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, can be reached at 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for unpublished applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions about access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this Ex parte Reexamination proceeding should be directed to:

By Electronic Filing System (EFS:

Registered users may submit via the electronic filing system EPS-Web at
https://efs.uspto.gov/efile/myportal/efs-registered

By Mail to:

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Central Reexamination Unit
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to:

(571) 273-9900
Central Reexamination Unit

By hand to:

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Randolph Building
401 Dulany Street
Alexandria VA 22314

For EFS-Web transmissions, 37 CFR 1.8(a)(1)(i)(C) and (ii) states that correspondence (except for a request for reexamination and a corrected or replacement request for reexamination) will be considered timely filed if (a) it is transmitted via the Office's electronic filing system in accordance with 37 CFR 1.6(a)(4), and (b) includes a certificate of transmission for each piece of correspondence stating the date of transmission, which is prior to the expiration of the set period of time in the Office Action.

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